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NEWER KNOWLEDGE CONCERNING THE INCEPTION OF PNEUMONIA AND ITS BEARING ON PREVENTION *

By O. H. ROBERTSON, M.D., *Chicago, Illinois*

DESPITE the many recent advances made in the recognition and detection of the etiological agents causing acute pneumonia, the problem of the origin of this disease is still unsolved. Evidence both clinical and experimental points to the air passages as the route of infection, but the question as to how the pathogenic microörganisms gain access to the bronchial tree and what conditions are necessary to cause pulmonary infection, remain largely unanswered. It is probably a significant fact that the bacteria causing pneumonia (chiefly pneumococci, streptococci, staphylococci) are normal inhabitants of the upper respiratory tract at one time or another. Although the most frequent incitants of typical lobar pneumonia—pneumococcus Types I and II—are not commonly found in the pharynx of healthy persons, such individuals may become carriers of these types upon exposure to cases of Type I and II pneumonia, and are particularly liable to become carriers if they are suffering from a cold at the time.[1] The other 30 odd types of pneumococci are found frequently and in many instances constantly in the normal throat, as are staphylococci and to a somewhat less extent hemolytic streptococci and Pfeiffer's bacilli.

Mode of Entrance of Bacterial Incitants of Pneumonia. The means by which pneumonia-inciting bacteria gain entrance to the airways of the lung would seem to be limited to inhalation of droplets and the passage of fluid down the larynx. How frequently pneumonia occurs as the result of simple inhalation of pneumococcus-containing droplets we do not know. Available evidence both clinical and experimental suggests that this is not the usual source of infection. Physicians and others attending pneumonia patients must inhale considerable numbers of air-borne pneumococci; yet, when such

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individuals are in good health, contact infection is rare. Attempts to produce pulmonary infection in normal animals by exposing them to atmospheres laden with droplets of pneumococcus culture have been unsuccessful. Stillman [2] placed mice in a chamber into which he atomized 50 c.c. of a highly virulent pneumococcus culture. In spite of their exposure for an hour to such an atmosphere none of the mice became infected. We have repeated these experiments using a Graeser [3] atomizer which dispersed the culture fluid into such fine droplets that they could penetrate to the pulmonary alveoli. Likewise, we were unable to produce pulmonary infection in the mice. Stillman was able to induce pneumonia by this means only when he employed mice that had been partially immunized to pneumococcus and intoxicated with alcohol before exposure to the air-borne microörganisms. However, there is evidence that pneumonia in man may be caused by inhalation of infected droplets. One such instance occurred in our laboratory. An assistant who was apparently in good health contracted lobar pneumonia on two separate occasions within 30 to 36 hours after accidental exposure to droplets of first Type I and then Type II pneumococci.[5]

It seems more likely, as I shall attempt to indicate, that the bacterial incitants of pneumonia are usually carried into the lungs by means of infected fluid exudate from the upper respiratory tract. Before presenting evidence for this view I would like to discuss briefly the various means by which the body protects itself against the entrance of foreign material into the lung and the mechanisms employed to eliminate such noxious matter which has penetrated the lower respiratory tract.* Much of the particulate material in the inspired air adheres to the mucus layer on the walls of the passages of the upper respiratory tract. Further deposition takes place on the walls of the bronchi. This mechanism of air clearing is so effective, especially in the case of dry particles, that relatively few of them reach the alveoli. It is only when dusts, carbon, silica particles, and similar materials are breathed over long periods of time in high concentration that they are found in any quantity in the air sacs. Small fluid droplets on the other hand apparently possess a much greater capacity to penetrate to the depths of the lung. Stillman and Branch [4] exposed rabbits and mice to atmospheres containing droplets of streptococci, pneumococci and staphylococci, and were able to recover these microörganisms from the periphery of the animals' lungs. Likewise, Hamburger and the author [7] recovered pneumococci from the peripheral lung tissue of dogs within five minutes after subjecting them to an intrabronchial spray of pneumococcus culture.

The principal mechanism for the expulsion of foreign matter from the lung is that of ciliary action which is capable of sweeping along particles at a surprising rate, 0.25 to 1 cm. per minute in the bronchi and up to 3 cm. in the trachea.[8] The effectiveness of the cilia is dependent upon an intact mucus layer as shown by Proetz.[9] When this layer is broken by drying or chemical

* This subject has been dealt with at length by the author in a recent review of the literature (Physiol. Rev., 1941, xxi, 112).

action ciliary movement ceases. The narrowing and widening of the diameter of the bronchi with each respiration, the possible peristaltic movements of the bronchi, and cough all aid in the eliminatory process by way of the trachea. However, when extraneous material enters the terminal units of the airways, the alveoli, it is disposed of much less easily since the alveoli contain no cilia or musculature. The chief means employed by the body for the immobilization and removal of foreign matter in this locus is that of phagocytosis by certain large ameboid cells, the alveolar phagocytes or "dust cells" of Von Inns, normally present in small numbers in the alveolar spaces and mobilizable in large numbers in response to certain types of stimulation. Under ordinary conditions these several clearing mechanisms are so effective in the removal of particulate matter that the lungs of normal human beings are for the most part kept sterile.

Barrier of the Epiglottis. Fluid entering the lower respiratory tract is distributed in a manner quite different from that of air-borne material. Liquids passing the barrier of the epiglottis tend to flow directly to the terminal parts of the lung, depending upon the viscosity of the fluid and the position of the body, and are expelled much less easily than particulate matter. The fact that the epiglottis constitutes by no means a perfect barrier to the passage of material from the upper to the lower respiratory tracts has been appreciated only in recent years. Clinicians have long felt that the pathological condition of bronchiectasis was due principally to the implantation within the bronchi of infected exudate from locally diseased areas in the nose and throat. But it was not until the relationship between lipoid pneumonia and oily nose drops was recognized by Laughlin in 1925 [10] that this subject received special investigation. The experiments of Walsh and Cannon [11] demonstrated clearly that liquids dropped into the nasal passages of animals quickly found their way into the depths of the lungs and if irritating in nature, produced an inflammatory reaction in the alveoli and lung parenchyma. Webster and Clow [12] were able to produce pneumonia in mice by the nasal instillation of pneumococcus culture.

Conditions which cause failure of the epiglottis to close completely are not well understood, but an important contribution to our knowledge has recently been made by Nungester and Klepser.[13] These workers, by means of an ingenious technic, measured the closure of the epiglottis in rats and found that lowering the surface temperature of the animal resulted in incomplete closure. Under such conditions they found that India ink, mixed with a moderately viscous mucin preparation and placed in the nares, found its way into the lungs in considerable quantities in more than half of the test (chilled) animals, whereas in the normal non-chilled controls very little or no ink was detected. Using the same technic they were able to induce pneumonia in chilled rats by the nasal instillation of pneumococci suspended in mucin in 42 per cent of the rats, whereas infection occurred in only 13 per cent of the non-chilled controls similarly injected. Like results were obtained by anesthetization with alcohol or ether.

Investigation of Conditions Favoring the Inception of Experimental Pneumonia

With these preliminary data before you I wish to proceed now to a brief account of an investigation which my associates and I have been conducting with the intent of determining some of the conditions within the lung which favor the inception of pneumococcus pneumonia. Although it is not unlikely that changes, both general and local, play a rôle as so-called predisposing factors, such experimental and clinical observations as are available suggest that local changes are the more important of the two. Since our study has dealt with experimental pneumonia in the dog, it will be necessary first to describe the chief characteristics of this canine disease which simulates closely clinical lobar pneumonia. Making use of such knowledge as was available concerning the inception of lobar pneumonia, namely, that it is primarily a localized infection presumably produced by pneumococci implanted in the terminal airways, and that certain conditions such as chilling acted as predisposing factors, we were able to produce pneumonia in dogs by means of injecting pneumococci suspended in a viscous starch medium into a terminal bronchus. The animals had been given a dose of morphine beforehand sufficient to lower the body temperature three to five degrees. After six to 12 hours there was a marked rise in temperature and blood count, and later, signs of consolidation both by roentgenogram and physical examination appeared. The temperature elevation was sustained three to five days, then dropped abruptly with the onset of recovery. The lesion remained localized to the infected lobe in many instances, but not infrequently spread to other lobes.[14] The occurrence of bacteremia, the degree of pulmonary involvement, and the outcome were found to depend largely on the size of the infecting dose. The prognostic significance of bacteremia, changes in the white count and extent of pulmonary involvement, were the same as in clinical pneumonia.[15] The gross pathological and microscopical examination of the lesions exhibited a striking resemblance to those of human lobar pneumonia in all stages of the disease.[16]

Although we were able to produce experimental pneumonia regularly by this means even with minute doses of pneumococcus culture, the procedure is a highly artificial one and left open the question as to what relationship this might bear to the problem of the inception of pneumonia in the human being. We felt that the problem could be approached most profitably by way of a study of the origin of secondary lesions occurring spontaneously during the course of experimental canine pneumonia, since it seemed possible that the local conditions responsible for a new lobar lesion might be of the same general nature as those concerned in the initiation of the primary infection.

Mechanism of Interlobar Spread. Little is known of the mechanism by which interlobar spread takes place, either in human lobar pneumonia or in the experimental disease in the dog. The view generally held and an eminently reasonable one, is that new lesions arise as a result of the aspiration of

infected exudate or sputum from the primary lesion, but this conception fails to account for the manner in which the tenacious viscid material reaches the smaller bronchi of another lobe and initiates infection. In our study of the evolution of the lesion of experimental pneumococcus pneumonia in the dog, the margin of the growing lesion from a very early stage was observed to consist of edema-filled alveoli containing pneumococci (figure 1).[17] A

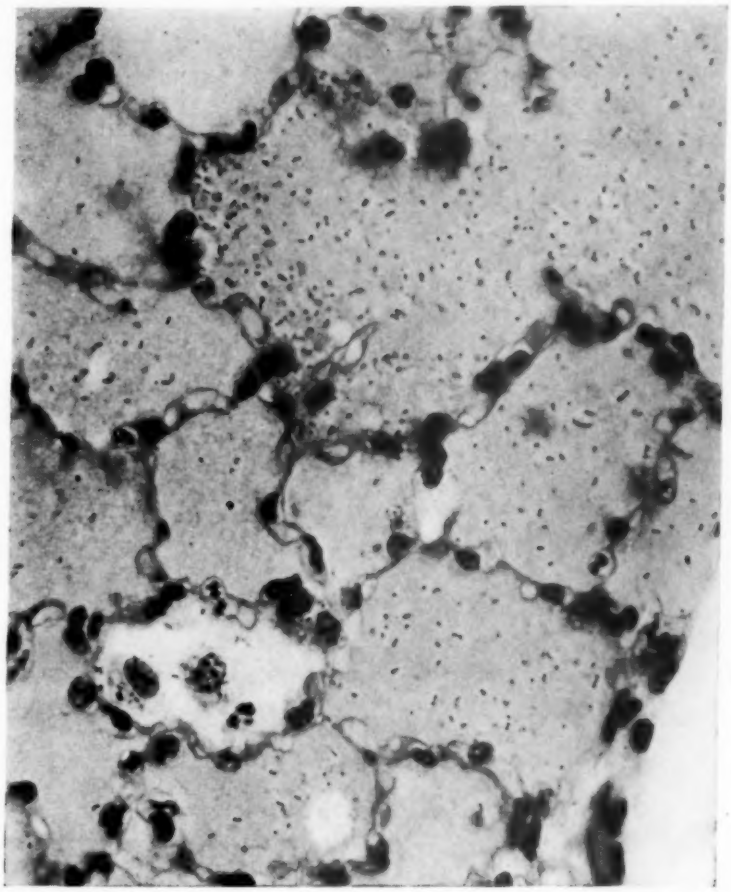

FIG. 1. Photomicrograph of pneumococcus—containing edema fluid present at the margin of spreading lesions and also found here and there in the terminal air-ways of uninvolved lobes of dogs showing metastatic lesions elsewhere in the lung.

similar picture is exhibited by the younger spreading lesions in the lungs of patients dying of lobar pneumonia. The amount of edema in the experimental lesion was found to depend largely on the size of the infecting dose. Lesions produced by doses of culture which result in a high mortality are much more edematous than those produced by smaller inocula from which the animals usually recover. Not infrequently the bronchi of such wet lobes,

when observed through the bronchoscope, are seen to be filled with foamy edema fluid. In this respect the amount of edema in the initial lesion is related to the incidence of spread, since metastatic lesions occur much more frequently in animals infected with the larger dosage.

In support of the concept that edema fluid may play the principal rôle in the transport of pneumococci from one lobe to another by way of the air passages, is the observed sequence of interlobar spread in canine pneumonia as related to the anatomical arrangement of the bronchi and the prone position of the dog. The relative positions of the main stem bronchi are shown in the accompanying photograph of a Wood's metal cast of the dog's

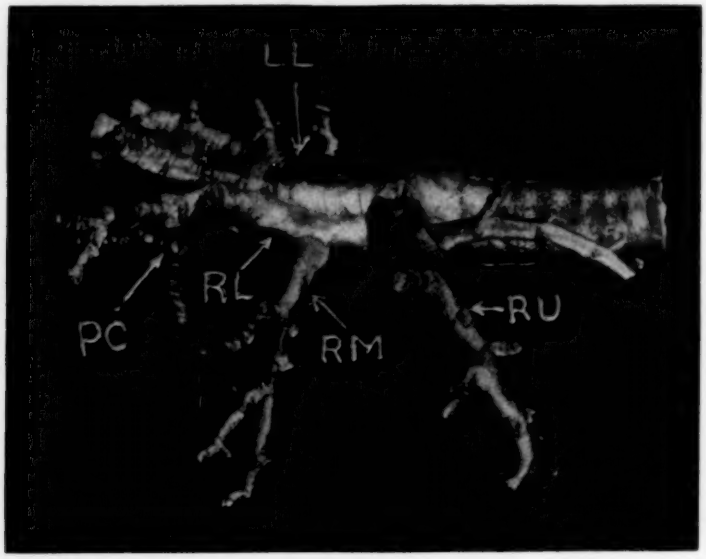

FIG. 2. Wood's metal cast of the bronchial tree of the dog as seen from the right side with the animal in the standing position. The different lobes of the dog's lung are indicated as follows: R.U. = right upper; R.M. = right middle; R.L. = right lower; L.L. = left lower; P.C. = post cardiac. For the purpose of clearer representation the left upper lobe bronchus has been deleted from the photograph.

bronchial tree (figure 2). The direction of interlobar spread in the dog is fairly regular. When infection is initiated in the right lower lobe with a dose which ordinarily leads to multilobar lesions, the right middle lobe, whose bronchus opens into the floor of the right main stem, is the second to become involved. Next in order of involvement are the right upper and postcardiac lobes, the respective bronchi of which leave the lateral walls of the right main bronchus and the right lower lobe bronchus. The two lower lobe bronchi are inclined at a slightly upward, i.e., dorsal angle.

With the initial lesion in the left lower lobe, the second lobe most often involved is the left upper. The bronchus to this lobe opens into the floor on the lateral side of the left main stem. When spread to the opposite side

occurs, it is almost always in the upper or middle lobes. The opposite lower lobe is with a rare exception the last to become involved.

Thus the anatomical arrangement of the bronchi, together with the fact that the dog with pneumonia lies in his cage most of the time with the head and upper thorax at a somewhat lower level than the rest of the body, affords easy opportunity for pneumococcus laden edema fluid to flow into the middle or upper lobes. However, we do not know to what extent such intrabronchial flow of infected exudate actually occurs. Is this material continually penetrating to the depths of the uninvolved lobes in all cases of pneumonia to a greater or lesser degree? In animals with non-spreading lesions is it quickly eliminated, or in such instances does the exudate (probably small in amount) fail to reach the terminal airways?

In order to ascertain the distribution of pneumococci in the lungs of dogs with non-spreading and spreading lesions, multiple cultures were made of the peripheral areas of all the lobes of the lungs, both normal and obviously involved. Briefly, it was found that in dogs with single lobe lesions, pneumococci were recovered from the lesion itself but not from any other part of the peripheral lung tissue, whereas in animals showing spread to other lobes, microörganisms were found to be distributed widely throughout the lung in both normal appearing and consolidated lobes. Some of the microscopic sections of the uninvolved parts of the lungs of dogs with metastatic lesions elsewhere revealed small masses of pneumococcus-containing exudate in the smaller bronchi and terminal airways of otherwise normal tissue. This finding would seem to provide direct evidence for the manner in which pneumococci are transferred from the initial lesion to other lobes and highly presumptive evidence for the mode of origin of the secondary lesions.[18]

Artificial Production of Secondary Pneumonic Lesions. If this were the correct interpretation of the mechanism of interlobar spread it should be possible to induce secondary lesions by the intrabronchial implantation of fluid pneumonic exudate in dogs with primary lesions which ordinarily are not followed by extension to other lobes. Furthermore, it should be possible to predict the lobar distribution of such secondary lesions by arranging the position of the animals so that the injected fluid would be carried by gravity into the most dependent bronchial opening nearest the point at which the exudate was deposited.

To carry out experiments of this kind fluid exudate was aspirated from the lesions of dogs infected with large doses of pneumococcus culture, both from the living animal and from the excised lungs of such dogs. The exudate which contained large numbers of pneumococci was injected by means of a rigid, small bore metal catheter inserted through a bronchoscope. An example of the result of such deposition of infected pneumonic exudate in the trachea or bronchi is shown in figure 3. This animal, infected with 0.00001 c.c. of pneumococcus Type I culture in the right lower lobe, exhibited at the end of 24 hours consolidation of the entire lobe. By 48 hours, roentgen-ray showed no further extension of the pathological process. With

the intent of producing a secondary lesion in the left upper lobe, the animal was placed on its left side with the head elevated approximately 20° and 0.25 c.c. pneumonic exudate injected into the trachea about three inches above the carina. This position was maintained for 40 minutes. That the exudate flowed into the infected bronchial opening was revealed by the roentgenogram made on the following day. Autopsy showed consolidation of most of the left upper lobe, as indicated in the diagrammatic representation of the excised lung.

In this way secondary lesions were artificially induced in various lobes of the dog's lung by placing the animal in an appropriate position. Likewise, it was found possible to produce lobar pneumonia regularly in normal dogs by the same technic.

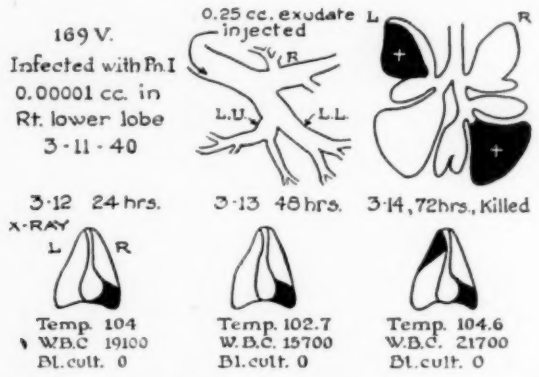

FIG. 3. Production of a secondary lesion of the left upper lobe in a dog with a 48-hour primary lesion in the right lower lobe. The black areas in the diagrams of the roentgen-rays and the postmortem lungs represent consolidation. The plus sign indicates positive cultures of pneumococcus.

Control experiments on the fluidity of the exudate revealed the fact that if a viscous exudate were injected either intrabronchially or intratracheally, secondary lesions did not result. Furthermore, if the position of the animal at the time of the intratracheal injection of even a very fluid exudate was such as to favor flow away from the bronchial openings, no lesions occurred.[19] The infectious material was presumably eliminated through the epiglottis.

The question arises as to what relationship these findings in the canine disease bear to the problem of interlobar spread in the human being. As indicated at the beginning of this discussion, the developing lesions of clinical lobar pneumonia exhibit the same peripheral zone of infected edema fluid which characterizes the canine lesion. Possibly the best evidence that the same mechanism of interlobar spread operates in the human patient as we believe occurs in the experimental animal lies in one conspicuous difference exhibited by the two diseases in the sequence of progressive lobar involvement. Whereas spread to the opposite lower lobe occurs commonly in human pneumonia [20] and constitutes by far the most frequent bilobar in-

volvement, it is rarely seen in the dog until after all the lobes on the side of the initial lesion have become involved. The semi-reclining position of the pneumonia patient would favor the gravitation of infected edema fluid into the lower lobe bronchi, whereas the prone position of the dog would have the reverse effect. Certain anatomical differences between the lungs of man and dog, aside from the position of the bronchi, make any exact comparison of the sequence of interlobar spread impossible.

Experimental Evidence as to the Relative Rôles Played by Obstruction and Irritation in the Inception of Pneumonia

In addition to clarifying to a considerable degree the mechanism of the origin of new lesions during the course of pneumococcus pneumonia, the results of the foregoing experiments suggested that certain conditions are essential for the production of the pneumonic lesion: first, the implantation of pneumococci in the terminal airways; second, a fluid but viscous medium which prevents their rapid expulsion from this region of the lung; and third, the presence of local irritation such as is produced by sterile starch and also probably by the fluid pneumonic exudate which contains the edema producing substance described by Sutliff and Friedemann.[21]

In order to determine whether obstruction alone is sufficient to initiate a lesion, pneumococci were forcefully sprayed through a bronchoscope into the lower lobes of normal dogs. Following this procedure a small quantity of a viscid starch paste or mucin was injected into a terminal bronchus of one of these lobes. Pneumonia seldom resulted in these animals.[22] This made it seem evident that obstruction per se was not the principal factor, although we had no means of knowing whether the number of pneumococci trapped by the obstructing mass in any one locus was sufficient to initiate a lesion. Earlier observations indicated that a certain minimum number was necessary to produce infection.

Experiments were then planned with the purpose of testing the relative rôle played by local obstruction and irritation in the inception of canine pneumonia. Two parallel series of animals were injected with the same dose of pneumococci. In one series the microörganisms were suspended in an irritating, and in the other a non-irritating medium. For the non-irritating medium we made use of the device employed by Loosli [23] for the demonstration of the natural occurrence of interalveolar pores, namely, the dog's own citrated plasma which was recalcified just before injecting it into the lung. Within a minute or two after reaching the terminal airways, the plasma clotted and fixed the pneumococci in the alveoli. Five per cent starch broth paste, as ordinarily used to produce the experimental infection, was used in the other series. Sterile starch alone will produce a small localized hemorrhagic lesion. In vitro tests showed that the pneumococci grew just as well in the clotted plasma as in the starch.

It was found that all the 12 animals injected with the starch-pneumococ-

cus mixture developed pneumonia characterized by the consolidation of a whole lobe or more, whereas none of the dogs receiving the same dose of pneumococcus culture suspended in plasma became infected. When killed 24 hours after injection the lungs of these latter animals showed only small areas of atelectasis at the site of infection which were usually sterile on culture. In a second experiment of the same kind a much larger infecting dose was employed. Almost half the dogs injected with plasma in this series developed pneumonic lesions, indicating that if a sufficient number of microorganisms are trapped in the terminal airways obstruction alone may be sufficient to produce infection.[24]

Relationship of Experimental Findings to Possibilities of Prevention of Pneumonia in Human Beings

What bearing do these experimental findings have on the occurrence of pneumonia in human beings? Since the common cold or upper respiratory infection is by far the most frequent antecedent of pneumonia, this condition should be considered first. It is well known that during the course of a cold the bacterial flora in the upper respiratory tract increases markedly.[25] If, in addition, the patient acquires types of pneumococci other than those he habitually carries, especially Types I and II, the chances for lower respiratory infection are increased. Then all that is needed for implantation of pneumococci or streptococci in the lung is the passage of sufficient fluid exudate past the barrier of the epiglottis. The added factor of irritation of the lower respiratory tract may be present as indicated by the finding of fine râles in the lungs in certain cases of severe colds. Although we do not know certainly how to prevent the occurrence of pneumonia following a cold, adequate care of the infection and especially an awareness of the rôle played by chilling and the danger of acquiring the more highly pathogenic types of pneumococci from other individuals during exposure to crowds, would, I believe, help in reducing the incidence of pneumonia.

Postoperative Pneumonia. There is, however, another predisposing condition on which the results of the foregoing experiments have an important bearing, namely, surgical operations with general anesthesia. The occurrence of postoperative pneumonia, unhappily all too frequent, appears to be due to the aspiration of infected fluid either with or without attendant pulmonary atelectasis. The relationship of general anesthesia to incomplete closure of the epiglottis has been pointed out earlier in the experimental findings of Nungester.[13] Just how much fluid from the upper respiratory tract reaches the bronchi probably depends to a large extent on the amount of secretion present in the pharynx. The presence of an upper respiratory tract infection at the time undoubtedly increases the possibility of implantation of infected exudate in the terminal airways. Indeed, the author has observed repeatedly the occurrence of postoperative pneumonia in patients operated upon at the time they had what was considered to be very mild upper res-

piratory infection. The first consideration then is to defer operation, if possible, in any patient who shows the slightest sign of an infection in this region. A second preventive measure is that of clearing out as completely as possible at the termination of the operation all secretions from the pharynx and larynx. Following this, advantage should be taken of the effect of gravity in aiding elimination of foreign material from the lung. Elevation of the foot of the bed for several hours postoperatively would assist the patient to get rid of such material as had been aspirated during the operation and also tend to prevent the flow of more fluid into the lung. The striking effect of postural drainage in cases of lung abscess indicates how marked an influence gravity exerts in aiding expulsion of fluid material from the bronchi.

The occurrence of postoperative pulmonary atelectasis always carries with it the possibility of infection since the effectiveness of the eliminatory mechanism of the atelectatic lobe is much reduced. Our experiments on the inception of canine pneumonia showed that although small numbers of pneumococci obstructed in the terminal air passage failed to produce pneumonia in the absence of local irritation, pneumonia could, however, be produced under such conditions if the number of implanted microörganisms was sufficiently large. It would seem not unlikely that postoperative collapse of the lung may be prevented by the same measures employed in its relief, namely, frequent changes in the posture of the patient from side to side and adequate ventilation of the lungs. Whether all patients following general anesthesia should be given inhalation of 10 per cent CO_2 and 90 per cent oxygen is a matter for the surgeon to decide, since there is much difference of opinion on this point; at any rate frequent deep breathing should be encouraged in one way or another. One of the most striking examples of the deleterious effects of immobilization of the patient after operation is seen in older persons following removal of cataract. During the four or five days that many ophthalmic surgeons consider it necessary to keep the patients on their backs, the posterior portions of the lungs ventilate relatively poorly, the functions of pulmonary elimination are depressed, and it is in these portions of the lungs that pneumonia not infrequently appears.

Postinfluenzal Pneumonia. A third antecedent of pneumonia is influenza. Whether the predisposing effect of this disease is of the same nature as that of the common cold is not known. It would seem likely, however, that irritation and injury of the lower respiratory tract play a much more important rôle in the inception of pneumonia complicating influenza.

Can postinfluenzal pneumonia be prevented by the use of sulfonamide drugs? This question cannot be answered now, since so little is known concerning the prophylaxis of pneumonia of any kind by chemotherapeutic agents. Several groups of workers have made studies of this subject in experimental animals. Gregg, Hamburger and Loosli [26] administered sulfapyridine by mouth to dogs during the 24 hours preceding experimental intrapulmonary inoculation with pneumococcus Type I. The dosage of drug

varied but it was sufficient to produce an adequate concentration of sulfapyridine in the blood. All these animals developed pneumonia which at the end of 24 hours occupied a whole lobe, just as seen in the untreated dog. Their studies were not carried sufficiently far to determine whether chemotherapy begun before infection is more effective in controlling the course of experimental canine pneumonia than when such treatment is begun after the disease has been initiated.* Goldstein and Graef,[28] working with experimental pneumococcus pneumonia in rats, were also unable to prevent the disease by administering sulfapyridine before infection. Hochberg and coworkers [29] reported partial success in preventing experimental pneumococcus pneumonia in dogs by the prophylactic use of sulfapyridine, but their method of inoculation is open to the objection that it does not produce pneumonia regularly.

These results do not encourage us to believe that pneumonia in the human being can be prevented by chemotherapeutic agents. But certain practical considerations arise in relation to postinfluenzal pneumonia if and when we should have an epidemic of the 1918 type. The very low incidence of pulmonary complications in the recent influenza epidemic would certainly not justify the general use of chemotherapy in cases of influenza even though we possessed definite evidence that pneumonia could be prevented by this means, and there is no evidence that influenza itself is affected by any of the sulfonamide series. In the presence of an epidemic of severe influenza, on the other hand, the situation would be altered. Statistics of the pandemic during the previous world war showed that approximately 20 per cent of influenza patients developed secondary pneumonia of bacterial etiology. Roughly one-quarter to one-third of these pneumonias ended fatally. Hence, at least 5 per cent of persons contracting influenza died. Even under such conditions I believe the ideal procedure would be close observation of the patients and administration of chemotherapy at the first sign of pneumonic complications, since these drugs act very quickly and effectively in the early stages of pneumonia. However, under conditions of a severe epidemic adequate medical observation is difficult or impossible and it may well be considered advisable to treat all influenza patients with chemotherapy.

Summary

In considering the means by which pneumococci and other bacterial incitants of pneumonia are carried into the lungs, evidence both clinical and experimental suggests that the escape of infected fluid exudate from the upper respiratory tract past the epiglottis plays a much more important rôle in the inception of pulmonary infection than does the inhalation of bacteria-

* Sulfapyridine and sulfadiazine have been found to be very effective in the treatment of experimental pneumococcus pneumonia in the dog.[26, 27] In a further series of experiments carried out in this laboratory an unusually severe test was made by selecting for treatment only those dogs with a bacteremia of more than 1,000 colonies per c.c. of blood. Almost 50 per cent of 22 such animals recovered whereas not a single dog out of more than 100 controls showing similar degrees of bacteremia survived.[27]

containing droplets. Experimental observations on pneumococcus pneumonia in the dog showed that not only does spread to other lobes occur as a result of the flow of infected exudate from the primary lesion by way of the bronchi, but that secondary lesions may be artificially induced by the deposition of such exudate in the trachea when the position of the animal is such that it favors flow of fluid into the bronchial openings. Furthermore, primary lesions can be initiated in normal dogs by the same procedure. Conditions necessary for the inception of infection appear to be (1) the implantation of microörganisms in the terminal air ways, (2) obstruction to their elimination, and (3) local irritation or injury. Experiments designed to compare the relative importance of obstruction and irritation indicated that local tissue irritation was the more decisive of the two factors in determining whether or not infection occurs.

The bearing of these observations on the prevention of pneumonia was discussed. Certain of the experimental findings, especially the effect of gravity on the flow of exudate in the respiratory tract, and recognition of the influence of general anesthesia on the closing of the epiglottis, seem to provide some general indications for the prevention of postoperative pneumonia. The possibility of preventing the occurrence of pneumonia by sulfonamide drugs does not seem very hopeful in view of the failure of such attempts in the experimental animal. However, under conditions of a severe epidemic of influenza of the 1918 type, such a procedure might well be considered advisable.

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AVIATION MEDICINE—A BRIEF HISTORY: THE PHYSICAL QUALIFICATIONS FOR FLYING; OXYGEN WANT AND THE USE OF SUPPLEMENTARY OXYGEN *

By Louis H. Bauer, M.D., F.A.C.P., *Hempstead, New York*

One of the newest specialties in medicine is that known as Aviation Medicine. It is a little different from other specialties in that it, to a large extent, comprises portions of other specialties all applied to aeronautics. It includes a certain amount of ophthalmology, otology, internal medicine, neuropsychiatry, psychology and a large amount of physiology. The whole purpose of the subject is largely preventive in nature. It involves the selection and care of the pilot and his protection against the physical forces acting upon him in the air, all with a view to preventing accidents from a physical cause.

Aviation Medicine had its origin in the first World War. The early experiences of the Allies indicated that the usual physical examinations were inadequate and that the stress and strain of flying were wearing pilots out at too rapid a rate. Little was understood about the effects of high altitude or long flying hours. Considerable information had been amassed by the time the United States entered the war and this country was able to profit by the experience of her allies. A research laboratory was established in 1917 and a great deal of experimental work was carried out there on problems of the eye, ear, physiology, psychology, altitude in general and oxygen supply apparatuses. A group of specialists drew up a physical examination outline based on what knowledge and experience were available at that time. Of course, many changes in the standards and methods of examination have been made in the past 25 years, but nevertheless, the sagacity of those early workers is illustrated by the fact that the basis of the present examination has very definite roots in the original one.

Following the war there was a slackening of interest and progress. Then in 1926 the Air Commerce Act was passed by Congress and civil aeronautics started on its noteworthy career. Physical standards again had to be revised, as civil flying does not call for quite the same qualifications as military flying. Interest again awakened in aviation medicine, and although progress was slow at first it developed momentum and by the time the second world war broke there was a widespread interest in it. The development of high speed flying and the invasion of extremely high altitudes brought new problems, not only of oxygen want and supply but of acceleration and deceleration and of low barometric pressure.

In the first war the problem was to find a machine that could keep up with

* Read at the St. Paul meeting of the American College of Physicians April 20, 1942.

the man, but in this war it is to find a man who can keep pace with the machine.

The military pilot is exposed to altitudes of 30,000 to 40,000 feet, to temperatures as low as 67° below zero, to speeds of 500 miles an hour, to intense glare, severe gales, to a constantly changing plane of equilibrium. In addition, he must operate a complicated machine requiring concentrated attention. It is obvious that the pilot is subjected to mental and physical stresses not resulting from any other occupation. Such being the case let us now consider the physical qualifications accepted, more or less universally, as requisite for piloting aircraft.

The Eye. Good vision has always been considered extremely important. By good vision we mean normal vision both central and peripheral. The pilot must be able to see not only straight ahead but on all sides. It has been said that the pilot should really have eyes in the back of his head as well. Originally, normal vision without correction was considered essential and this still holds for the military pilot as he flies often in open ships where glasses are a hazard. For the commercial pilot normal vision with correction is acceptable provided he has a reasonable amount of vision without correction. For the private or sport flyer the only requirement is that his vision must correct approximately to normal. Peripheral visual fields must also be normal. Aircraft must be picked up out of the "tail of the eye" by the military pilot.

Another most important qualification is the ability to judge distance. This is necessary in landing, taking off and in flying in formation, where the tips of the wings of the planes are often only a few feet apart. It requires binocular vision. Distance cannot be accurately judged with one eye.

Normal color vision is necessary in detecting colored markings on planes, colored signal flares and lights, navigating lights and the character of the terrain. A green-brown color confusion is a not uncommon form of color blindness, and interpretation of the different shades of green and brown is of material assistance in determining the nature of the terrain.

Ocular muscle balance is tested because latent defects may become manifest or cause distress under the influence of fatigue or low oxygen.

A certain accommodative power is essential to read maps or the instrument board.

The eyes and their appendages are examined for ocular disease which is disqualifying.

The Ear, Nose, and Throat. The elimination of all those with disease and obstructive conditions is necessary. Such conditions may light up into acute infections, interfere with free breathing, or by their toxic effects decrease adaptation to altitude and result in undue fatigue.

Hearing, formerly thought to be of little importance, has become of greater significance because of the increasing use of radio.

Equilibrium. This has in the past been a much discussed question. It is generally recognized now that in the pilot the most important factor in

equilibrium is vision and not the labyrinth. No matter how perfect a pilot's labyrinth, he is unable to maintain his ship on an even keel unless he can see the horizon or has learned to fly solely by instruments. Hence the Barany tests have been largely discarded and a simple test of self-balancing has been substituted. The Barany tests are useful, however, in demonstrating to a pilot the faultiness of the sensations derived from his labyrinth. In blind flying the pilot is taught to disregard his sensations and rely solely on his instruments. Equilibrium should be considered as a function of the whole proprioceptive mechanism, consisting of the eyes, ears, muscles, joints, skin, and viscera, from all of which certain sensations are derived assisting in maintaining balance, but the most important of these is vision.

General Physical Qualifications. This portion of the examination is similar to any thorough physical examination and is intended to eliminate both acute and chronic disease which would interfere with the safe handling of aircraft. A careful history is obtained. A history of asthma, malaria within five years, syphilis (unless there is serological evidence of cure), and encephalitis are all disqualifying per se. A history of other serious illnesses such as pneumonia, pleurisy, tuberculosis and the rheumatic group serves to call attention to the necessity of a very careful examination of the organs involved. Any acute illness is disqualifying, pending recovery, and any chronic disease resulting or apt to result in impairment of physical efficiency or which renders the applicant subject to recurrences or which will interfere with his tolerating the extremes of altitude, cold and fatigue to which he will be exposed, is also disqualifying. Particular attention is paid to structural defects. Limitation of motion or function of any extremity or joint may interfere with the manipulation of the controls necessary for the safe operation of aircraft. Special attention is given to the cardiovascular system. Not only are organic heart and circulatory disease disqualifying but vasomotor instability and neurocirculatory asthenia are also eliminated. One of the tests used on all military and air line pilots is the Schneider Index. This is a circulatory efficiency test and it is based on the reaction of the pulse rate and systolic blood pressure to changes of posture and exercise.

Neuropsychic Examination. It has been found that one of the commonest causes for grounding of pilots or for their inability to learn to fly, is a deficient neuropsychic make-up. Inability to relax, tenseness, poor emotional control are all common remarks on instructors' reports of "washed out" pilots. Hence, a very careful survey is made of the nervous system. This involves not only a neurological examination to eliminate organic neurological disease, but also a psychiatric examination, known as a personality study, which, in reality, is a survey of the entire mental life and reactions of the applicant. Effort is made to determine his past reactions to stress in the hope of assessing his probable reaction to stress in the future. It has been found that the stress and strain of flying affect the nervous system

sooner and more severely than any other system. A sound, stable, neuropsychic makeup is essential. Aeroneurosis, which is much the same thing as neurocirculatory asthenia, is very prone to develop in those with any constitutional psychopathic inferiority.

It might seem that such a thorough examination covering the eyes, ears, nose, throat, equilibrium, general physical condition and neuropsychic makeup ought to be sufficient. Unfortunately, however, it is not. Many men selected by this type of examination never learn to fly. The reason is a lack of what has been arbitrarily termed "flying aptitude." When the examination is made by a skilled flight surgeon who has had thorough training and extended experience in aviation medicine, the percentage of those still unable to grasp flying is much less, but even then there are some. A great deal of research has been undertaken to find some means of assessing this aptitude. Up to the present moment no wholly satisfactory means has been found. Some tests which give promise are too complicated, require too expensive apparatus, or are too technical for routine use. Many workers are still delving into the problem and it is hoped that before long some satisfactory test can be unearthed which will give the solution.

One of the stresses to which any military or air line pilot is subjected is high altitude. This applies particularly to the military pilot. To understand the effects we must review a little physiology.

As we ascend from sea level there is a gradual fall in barometric pressure. The atmosphere at any level is composed of about 79 per cent nitrogen and a trifle less than 21 per cent oxygen. The oxygen pressure in the atmosphere then is 21 per cent of the barometric pressure for that level. For example, at sea level the total atmospheric pressure is 760 mm. Hg. With the oxygen percentage at approximately 21, the oxygen pressure in the atmosphere is approximately 159 mm. When we breathe air into our lungs it absorbs water vapor amounting to 47 mm. pressure and this must be deducted from the total atmospheric pressure. Hence, in the alveoli of the lung the total pressure is not 760, but 760–47 or 713 mm. Furthermore, the carbon dioxide pressure must be deducted and, too, the oxygen percentage becomes reduced about one-third before it reaches the alveoli, so that for all practical purposes the alveolar oxygen pressure at sea level is 14 per cent of 713 or 103 mm. Hg. Even this disregards the CO_2 pressure. As we ascend, the barometric pressure falls steadily and we have a constantly falling oxygen pressure. Oxygen pressure is what keeps us all alive. If it falls below a certain level we become inefficient, then unconscious, and finally we will die. At 10,000 feet the alveolar oxygen pressure has dropped to 65 mm. At 20,000 feet it has dropped to 40 mm., and so it continues to decline the higher we go. At these higher altitudes the blood becomes insufficiently saturated with oxygen and symptoms of oxygen want appear. The oxygen want causes deeper breathing. The deep breathing upsets the chemical equilibrium of the blood by washing out carbon dioxide from the blood

stream and an alkalosis develops. This alkalosis and lack of CO_2 then interferes with the dissociation of the oxygen from the hemoglobin in the tissues.

Aside from the deepened breathing the pulse accelerates and there are changes in the blood pressure. These changes vary. The systolic pressure may increase and the diastolic may decrease. Only one may change and either or both may suddenly break and the individual faint.

The effects on the central nervous system come on comparatively early. There is at first a stimulation, and this is followed by decreased attention and lack of coördination of the finer movements. These increase until judgment, memory and vision diminish and fainting occurs. The pilot is wholly unaware of these symptoms. Not only may he be completely inefficient but may actually lapse into unconsciousness without realizing anything is at all unusual.

Up to a certain point all symptoms may be eliminated by the use of supplementary oxygen. By increasing the percentage of oxygen in the inspired air one increases its pressure. The amount necessary to restore one to sea level condition increases gradually up to a level of about 32,000 feet. From there up 100 per cent oxygen is necessary and gradually there is again a falling available oxygen pressure and consequent inadequate saturation of hemoglobin. For example, at 44,000 feet the hemoglobin is only 65 per cent saturated. At 47,000 feet the barometric pressure has fallen to 100 mm. Hg. From this must be deducted the 47 mm. of water vapor pressure, leaving only 53 mm. total of possible oxygen and carbon dioxide pressure, even though the individual is breathing 100 per cent oxygen. At these extreme heights nitrogen is given off into the blood stream and hence to the alveoli, still further diluting the possible oxygen available, and leaks are bound to occur around any mask. Hence, we have a person breathing pure oxygen, suffering from extreme oxygen want and if he goes above that critical level he dies from lack of oxygen saturation and from the added factor of interference with oxygen dissociation in the tissue as already mentioned. For all practical purposes one should go above 40,000 feet only in a pressure cabin or in a pressure suit, within which the atmospheric pressure is artificially kept up to a level compatible with life, and above 47,000 feet he cannot go in any other manner. All flights in both airplanes and balloons above this level have been made in pressure cabins or similar devices.

To prevent any distress or the development of undue fatigue, oxygen should be used above 10,000 feet. Above 15,000 it is necessary for efficiency. At 25,000 feet the average person will become unconscious without it; above 35,000 feet he becomes increasingly inefficient even with 100 per cent oxygen; and above 47,000 feet he will die even with 100 per cent oxygen, unless he is in a pressure cabin or suit.

There are various ways of using supplementary oxygen, but the accepted way in this country is to use gaseous oxygen with a mask preferably covering both nose and mouth. In fact, such a mask is essential in the higher alti-

tudes. A nasal mask may be used for altitudes up to 25,000 feet but even here it is less efficient and wastes oxygen. Masks of the B. L. B. or similar type are the ones in general use.

At levels above 30,000 feet we have to deal with the effects per se of low barometric pressure. At these high levels nitrogen is given off in the blood and aero-embolism occurs. This is the same condition as that found in deep sea divers and Caisson workers, which has become known as the bends or Caisson disease. Also we have to deal with the tremendous expansion of intestinal gases at extreme altitudes. These matters and the factor of high speed will be discussed elsewhere.

SUCCESSFUL TREATMENT OF GOUT*

By ELMER C. BARTELS, M.D., F.A.C.P., *Boston, Massachusetts*

GOUT has received widespread publicity during the last 10 years, with most writers giving attention to all the various phases of the disease except the prevention of recurring attacks. We have in reality reached a point in the therapy of gout similar to that in diabetes if investigators in that field had continued to give their attention to the treatment of coma and not to its prevention. Significant is the fact that leading students of gout are at present at odds on the vital question as to whether the recurring attacks of gout can be prevented. Can the treatment be offensive or must it remain defensive? Besides the accepted fact that gout shortens life, the economic aspect indicates the dire need for some type of therapy to prevent loss of time and money (figure 1). An analysis of 14 patients who had suffered

Average duration of disease	11 years
Average loss of time from work	20 mos.
Average loss in salary	$3640.
Average medical expense	$489.

FIG. 1. Economic aspect of gout in 14 cases

from gout for an average of 11 years showed they lost an average of 20 months away from work, with an average salary loss of $3640 and with medical expenses of $489.

In the latest textbook on *Diseases of Metabolism*, edited by Duncan,[1] Bauer and Klemperer state: "It is unfortunate for both the patient and physician that interval therapy in the prevention of future attacks (of gout) does not exist." They admit that a high purine diet may be harmful in some cases but that the addition or omission of purine containing foods is probably ineffective in changing the clinical course of gout. They allow small amounts of alcohol and advise against the use of cinchophen. It is their opinion that a sympathetic understanding on the part of the physician is all that can be offered since recurring seizures defy all therapeutic efforts.

Hench[2] does not agree with this discouraging outlook for patients with gout. He believes that by faithfully adhering to well planned interval treatment, patients can reduce the number and severity of acute attacks and thereby reduce the chance of chronic gouty arthritis and perhaps the late manifestations and complications of the disease. His plan consists of a reduced purine intake, avoidance of alcohol and the intermittent use of "urate eliminants" when necessary. These latter substances include aspirin, sodium salicylate, neocinchophen or cinchophen. This combination of diet and drugs is directed at control of the hyperuricemia.

* Read at the St. Paul meeting of the American College of Physicians April 24, 1942.

There is a noteworthy absence in the literature on gout of any statistical studies giving the results of carefully observed interval treatment. It was this fact which Bauer and his coworkers used in discounting the results of those who advocate interval treatment. They wished proof of the value of interval treatment through a carefully controlled study of a sufficient number of subjects on a constant regimen in which the level of the blood uric acid was taken into consideration. The present study meets these investigative requirements.

Basis of Present Treatment. In 1935 Lockie and Hubbard [3] proposed the use of a high carbohydrate, low fat diet for the treatment of gout. Their suggestion was based on the fact that a high fat diet was found to provoke attacks of gout. Earlier (1925), Lennox [4] demonstrated that a high fat diet causes a retention of uric acid, which was confirmed by Adlersberg and Ellenberg,[5] and Lennox suggested the use of a low fat diet in the treatment of gout.

A. Low purine intake relieves overtaxed purine metabolizing mechanism
B. High fat intake increases tubular resorption of urates
C. High carbohydrate intake produces uric acid diuresis
D. Cinchophen produces uric acid diuresis

FIG. 2. Rationale of treating gout with low purine, low fat, high carbohydrate diet and cinchophen

The plan of treatment utilized in this study (figure 2) was begun at the Lahey Clinic early in 1937, a preliminary report of satisfactory results having been made in 1939.[6] It consists of a diet low in purine and fat and high in carbohydrate, to which is added the periodic administration of cinchophen. The mode of action of this regimen is multiple. Purine restriction relieves the overburdened purine metabolizing mechanism, the low fat intake prevents purine retention, and the high carbohydrate aspect of the diet tends toward the diuresis of uric acid. To the diet is added cinchophen to further uric acid elimination. The cinchophen is given at the beginning of treatment according to the plan of Graham [7] (7½ grains three times a day for three days a week) which has been popularized by Hench. Alcohol is not permitted since most students of gout recognize it as harmful.

As treatment progresses, periodic determinations of the uric acid are made at one to three month intervals, and when a reduction in the serum uric acid occurs the dose of cinchophen is reduced from three days a week to two, to one, and omitted entirely when the uric acid reaches a normal or near normal level. Patients understand that the diet is the basis of treatment and that it is to be followed indefinitely. However, if the uric acid continues at a normal level, a more liberal diet is given.

Acute attacks of gout have been treated (figure 3) by the intravenous injections of glucose in addition to the plan outlined. Since the diet is low in both vitamins A and B, these vitamins are added. At times in gouty arthritis physiotherapy is helpful and large tophi are removed, if troublesome.

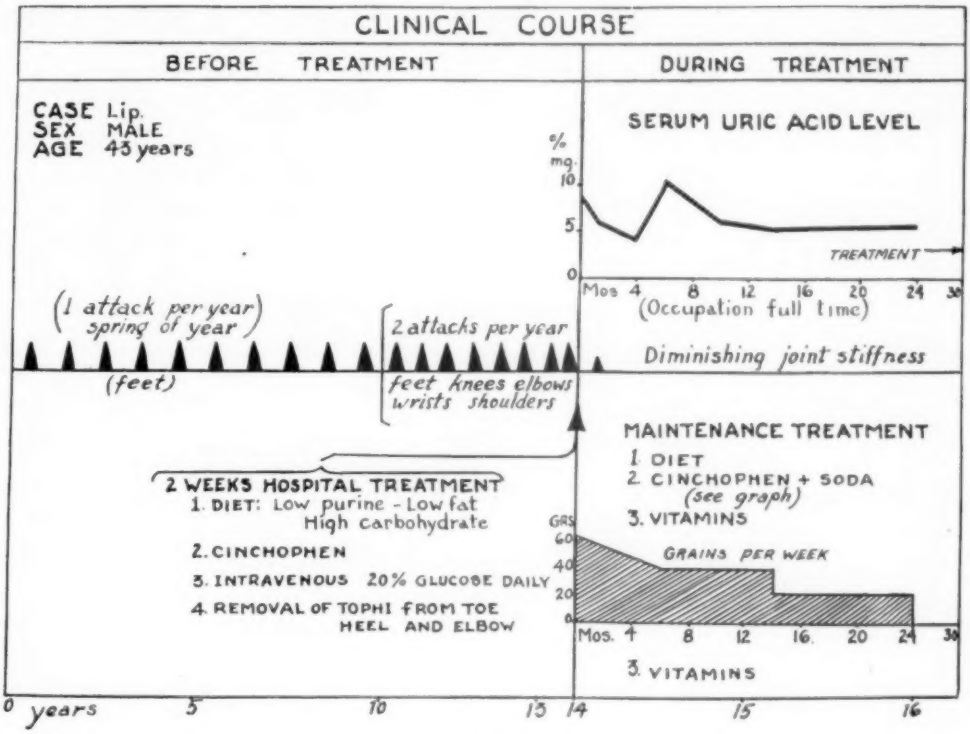

FIG. 3.

Patients Treated. Increasing numbers of patients with gout have come under our observation (table 1), and it has been possible to follow the course of many of these patients at frequent intervals. The results of treatment of 38 patients who were carefully followed are herewith reported. All of these patients with the exception of three were seen prior to January 1941. These three were included because they had had their disease for a sufficient

TABLE I

New Cases of Gout

Year	Number of Cases
1930	2
1931	2
1932	7
1933	2
1934	11
1935	12
1936	9
1937	12
1938	14
1939	21
1940	41
1941	50
Total	183

length of time to produce a constant pattern of attacks. All of these cases were followed up to January 1942.

Results of Treatment. These 38 cases have been divided into three groups. The first group includes 18 patients who have had the disease over nine years, in all of whom a pattern of attacks had been well established (figure 4). The second group contains 13 patients who have had the disease for seven years or less (figure 5). In both of these groups the diet plan was carefully adhered to and cinchophen was used in decreasing doses. In the

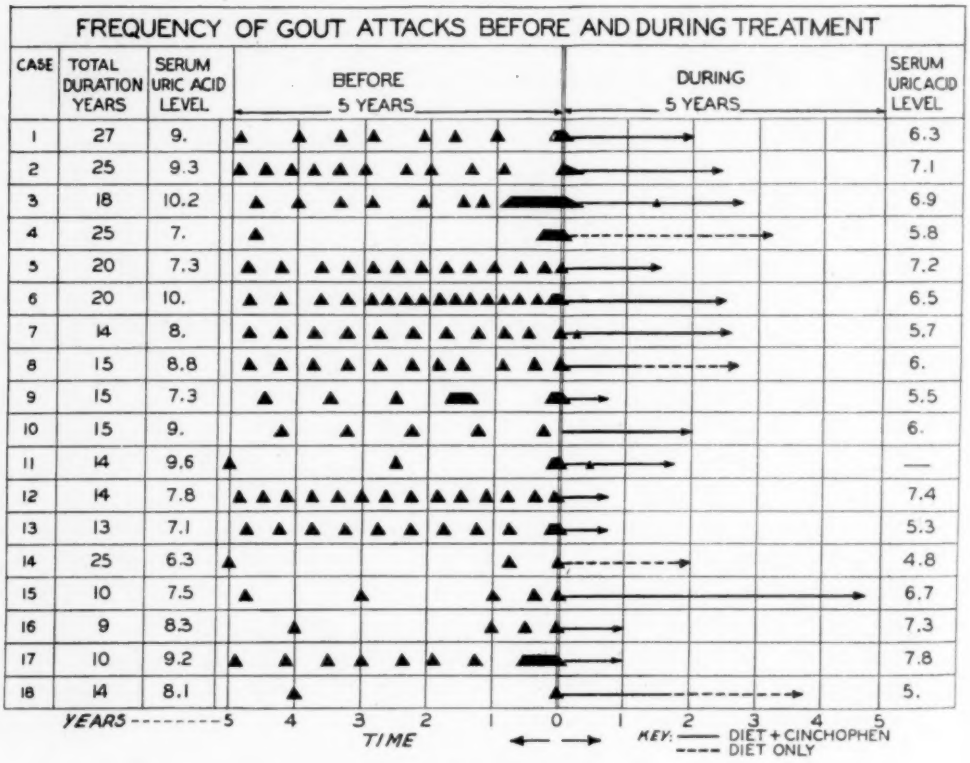
FREQUENCY OF GOUT ATTACKS BEFORE AND DURING TREATMENT
CASE
TOTAL DURATION YEARS
SERUM URIC ACID LEVEL
BEFORE 5 YEARS
DURING 5 YEARS
SERUM URIC ACID LEVEL
1 27 9. 6.3
2 25 9.3 7.1
3 18 10.2 6.9
4 25 7. 5.8
5 20 7.3 7.2
6 20 10. 6.5
7 14 8. 5.7
8 15 8.8 6.
9 15 7.3 5.5
10 15 9. 6.
11 14 9.6 —
12 14 7.8 7.4
13 13 7.1 5.3
14 25 6.3 4.8
15 10 7.5 6.7
16 9 8.3 7.3
17 10 9.2 7.8
18 14 8.1 5.
YEARS 5 4 3 2 1 0 1 2 3 4 5
TIME
KEY: DIET + CINCHOPHEN
DIET ONLY

FIG. 4.

third group (figure 6) have been placed seven patients who had the disease from three to 15 years. None of these patients followed the diet carefully, usually saying "50 per cent," and all used alcohol in varying amounts. Some of these patients took cinchophen, but without regularity.

The result of therapy in the first two groups was found to be satisfactory since two major requisites for successful therapy were met: (*a*) drop in uric acid level and (*b*) prevention of further attacks (figure 7). The 18 patients in the first group had suffered from attacks of gout for an average of 17 years, the longest time being 27 years. The serum uric acid level when they were first seen varied from 6.3 mg. per cent to 10.2 mg. per cent, the

average being 8.3 mg. per cent. These patients were treated for an average of two years, during which time there were only three minor episodes in the entire group as compared with 61 major attacks during an equal time before treatment. The uric acid level fell to an average of 6.3 mg. per cent. Diet

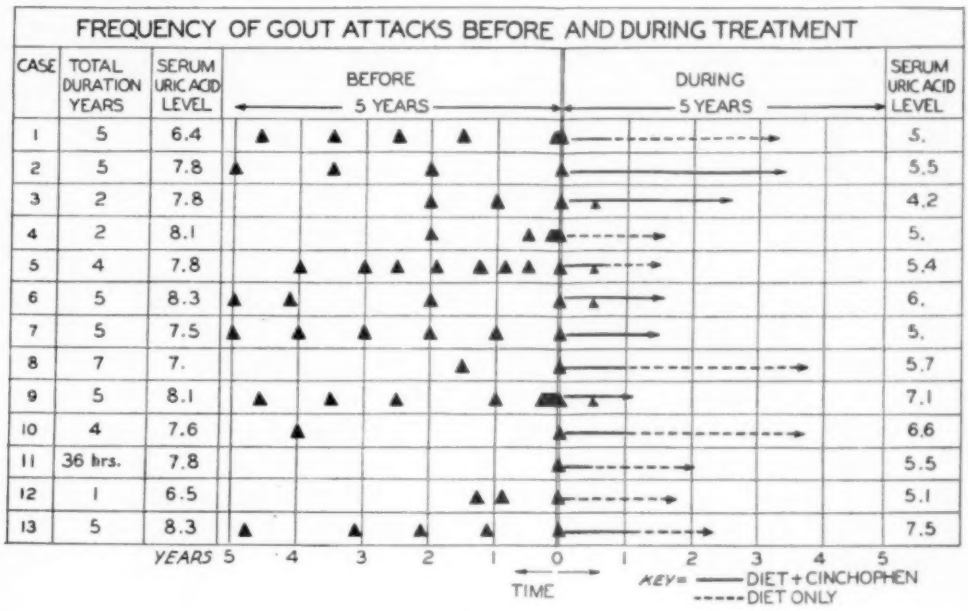

FIG. 5.

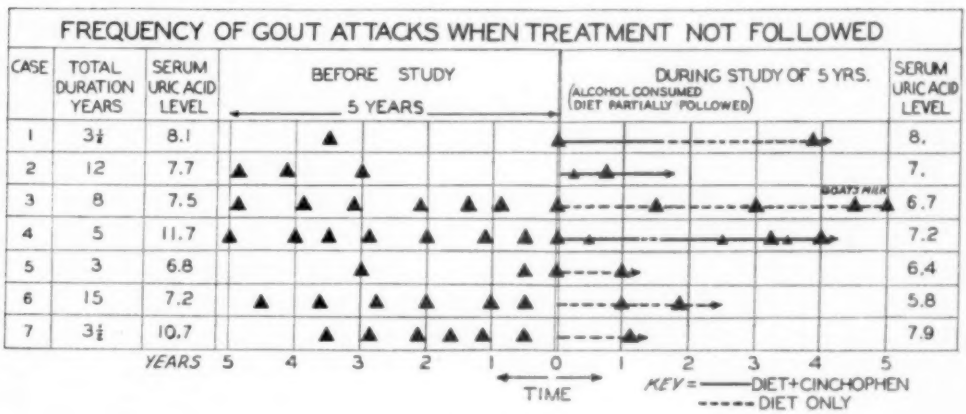
FREQUENCY OF GOUT ATTACKS WHEN TREATMENT NOT FOLLOWED
CASE
TOTAL DURATION YEARS
SERUM URIC ACID LEVEL
BEFORE STUDY
5 YEARS
DURING STUDY OF 5 YRS.
(ALCOHOL CONSUMED
DIET PARTIALLY FOLLOWED)
SERUM URIC ACID LEVEL
1 3½ 8.1 8.
2 12 7.7 7.
3 8 7.5 DIED OF HEART 6.7
4 5 11.7 7.2
5 3 6.8 6.4
6 15 7.2 5.8
7 3½ 10.7 7.9
YEARS 5 4 3 2 1 0 1 2 3 4 5
TIME
KEY= DIET + CINCHOPHEN
DIET ONLY

FIG. 6.

and cinchophen were used three-fourths of the total time the patients were treated and diet alone approximately one-fourth of the time.

The 13 patients in the second group had had attacks of gout over an average period of four years, with an average uric acid level on admission of

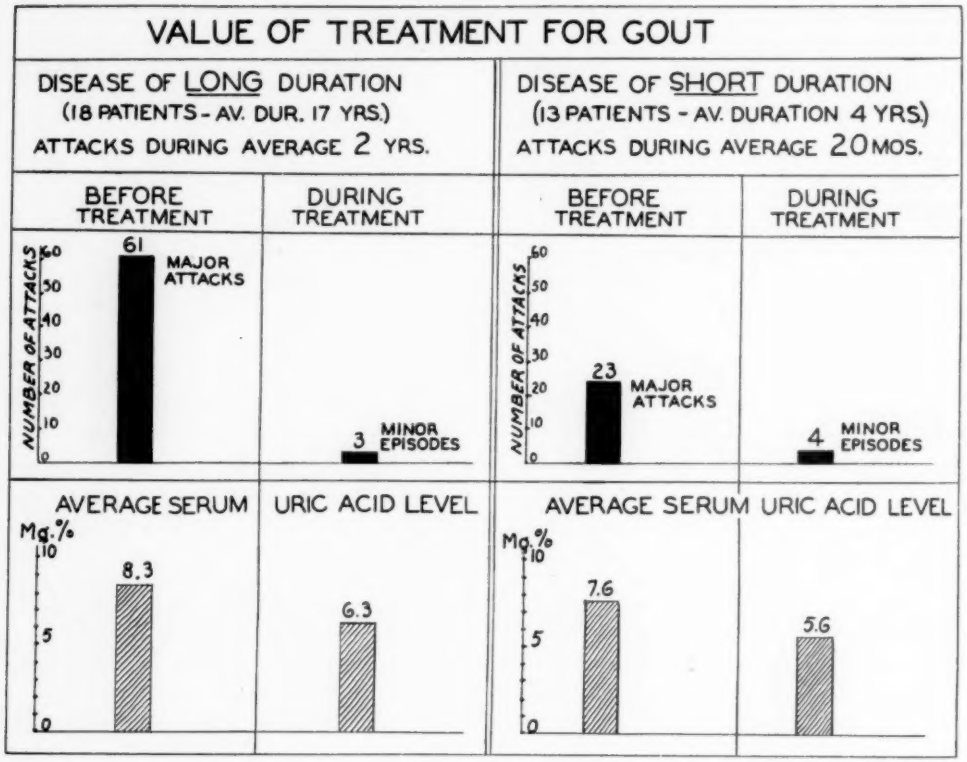

FIG. 7.

7.6 mg. per cent. In the average period of 20 months during which time these patients were treated, four minor attacks of gout occurred as compared with 23 major attacks during an equal period before treatment was begun. A combination of diet and cinchophen was used for practically the same length of time (16 patient years) as the diet alone (14 patient years).

Number of Patients	Average Duration Years	Serum Uric Acid Level Average mg. %		Frequency of Attacks During Average Period of 3 Years	
		Before Treat.	During Treat.	Before Treat.	During Treat.
7	7	8.5	7	23 major attacks	12 major 4 minor attacks

FIG. 8. Frequency of attacks when diet was followed only partially and alcohol was taken.

The seven patients who did not carefully follow the diet (figure 8) had attacks of gout for an average of seven years, the average value of serum uric acid being 8.5 mg. per cent. Over the average period of three years during which time their course was followed, 12 major and four minor

attacks took place. This number was half the number of major attacks (23) which had occurred during a similar period before treatment. The average uric acid level fell from 8.5 to 7 mg. per cent.

Little difficulty was experienced in having patients adhere to the diet plan. It was necessary to make rather drastic changes in the eating habits of a number of the individuals who were accustomed to large amounts of olive oil in their food. Repeated reviews of the diet were found necessary to prevent patients from making mistakes which they honestly did not realize they were making.

It is readily appreciated that the use of cinchophen in the management of these patients permits wide criticism in the face of the inherent toxic possibility of this substance. This fear may be overemphasized as in an analysis of the toxicity of cinchophen Hench reported finding only 250 such cases in the literature, and of these, only six patients had gout. He estimated a 1 to 60,000 chance of a toxic result from the use of this drug. In our use of cinchophen any possible chance of toxicity was minimized by certain factors: (*a*) patients were always advised as to the early toxic mani-

TABLE II

Serum Uric Acid Level and Non-Protein Nitrogen

Case	Serum Uric Acid Before Treatment	Serum Uric Acid During Treatment	Non-protein Nitrogen, mg. %	Clinical Progress
1	6.4	6.6	44	Good
2	8.0	7.1	55	Good
3	8.3	7.3	45	Good
4	8.0	6.7	45	Good
5	6.6	7.3	40	Good
6	9.2	7.5	43	Good

festations of the drug and told to discontinue its use if such occurred. (*b*) It was used only as an adjunct to careful dietary management. The dose of cinchophen was reduced as the level of uric acid fell, with the patient's knowledge that its use would at some time be discontinued. (*c*) Since the diet was high in carbohydrate it acted to fortify the liver against toxic agents. (*d*) In discontinuing alcohol, possible toxicity through the synergistic or intensified action of alcohol and cinchophen on the liver was avoided. (*e*) A moderate serving of meat, fish or fowl was given once a day in addition to other proteins to keep the protein intake at a proper level, this being another means of fortifying the liver against toxic damage. (*f*) In the last two years liver function tests, by the intravenous hippuric acid method, were made at intervals during treatment with cinchophen. In some instances cinchophen was stopped because the results of the liver function test fell below normal. Since renal damage may cause faulty results in the liver function test, care must be taken in its interpretation. In the first group, 14 of the 18 patients have continued to take cinchophen at least one day a week. In the second group, those of short duration, only five of 13 patients are now taking cinchophen.

A return of the serum uric acid level to normal did not occur in all cases (nine in the first group and three in the second group) in spite of the continued use of cinchophen. This was especially true in patients in whom the disease was of long duration. It was found that this failure usually occurred in patients who had renal insufficiency, as indicated by an elevated non-protein nitrogen (table 2). These six patients responded well to treatment, as indicated by failure of recurring attacks, in spite of continued elevated level of uric acid. In four of these patients there was a decrease in the uric acid level. Perhaps continued effort to return the uric acid level to normal by the use of cinchophen need not be exerted in patients with long-standing gout or in those in whom the uric acid level has been stabilized and symptomatic benefit has been obtained.

Perhaps sufficient time has not elapsed in all the cases reported to satisfy critical evaluation of the treatment from the standpoint of preventing further attacks, since it is well recognized that at times years may separate the recurring attacks. In patients in whom this criticism may be justified, a substantial drop in the level of the serum uric acid was always obtained, which is a prerequisite to the prevention of further attacks.

Summary

Indisputable benefit was obtained in a group of 31 patients with gout who carefully adhered to a low fat, low purine, high carbohydrate diet, with the addition of decreasing doses of cinchophen. On this plan of treatment seven minor attacks of gout occurred, as compared with 84 major attacks during a comparative period before treatment. This plan of treatment secured the desired results of reducing the blood uric acid level and reducing the number and severity of further attacks of gout. Even patients in the phase of chronic gouty arthritis responded to this plan of treatment. It is urged that this treatment be given further consideration by other physicians.

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A PROGRESS REPORT OF INVESTIGATIONS CONCERNED WITH THE EXPERIMENTAL TREATMENT OF HYPERTENSION WITH KIDNEY EXTRACTS *

By Irvine H. Page, M.D., O. M. Helmer, Ph.D., K. G. Kohlstaedt, M.D., G. F. Kempf, M.D., A. C. Corcoran, M.D., and R. D. Taylor, M.D., *Indianapolis, Indiana*

At this time last year we reported to you the reasons why we believe that certain extracts of normal kidneys contain a substance, or substances, which lowers arterial blood pressure in hypertensive dogs, rats and human beings.[1] It was pointed out that one of the most striking effects of these extracts was their ability to reverse the retinal arterial lesions observed during the course of the malignant phase of hypertension. Their administration was also often associated with a rise in the usually depressed renal blood flow.

Difficulties both in the preparation of the extract and in its use were numerous. The chief among the first were (1) extremely poor yields and (2) inadequate knowledge of the chemical nature of the active substances. Among the second were (1) pyrogenic reactions, and (2) occasional severe generalized reactions which appeared to be anaphylactoid in nature.

We have not believed that progress in the study of this highly complex problem would be made most rapidly by neglecting further studies on the mechanism of hypertension itself. For this reason investigations designed to elucidate the chemical structure of angiotonin have been actively pursued. Further work on the intrarenal hemodynamic changes in the kidneys in hypertensives has shown that so-called "renal ischemia" is not necessary for the persistence of renal hypertension.[2] Reduction of renal pulse pressure and, perhaps, moderate reduction in mean pressure seem to be adequate stimuli for its induction. This suggests that anoxia of the kidneys of marked degree is unlikely, at least in the early phase of hypertension. Thus, if the anaerobic decarboxylation of amino acids to form pressor amines, as suggested by the experiments of Bing,[3] is a part of the mechanism contributing to the maintenance of hypertension, it would probably occur late in the course of the disease. Other circumstances, as yet unknown, might, however, bring this mechanism into play during an earlier phase.

Evidence is steadily increasing that angiotonin plays an important part in the regulation of the arterial blood pressure both in normal and hypertensive subjects.[4] This is of some importance because during the past year we have attempted to assay renal extracts on the basis of their ability to destroy angiotonin. From this naturally springs the suggestion that the

* Read at the St. Paul meeting of the American College of Physicians April 21, 1942.

clinical effect of renal extracts is due to their ability to destroy circulating angiotonin. Attractive as this view may be, it remains unproved.

It is unnecessary to burden you with the story of the many failures we have had in attempts to purify kidney extract. A résumé is given of one method we are now actively investigating which may be of interest to those studying the subject themselves.

Preparation of Kidney Extract. Briefly, the steps involved are (*a*) extraction of the ground kidney with aqueous solution of acetic acid and salt, (*b*) raising the temperature to 56° C., (*c*) precipitation with ammonium sulfate to full saturation, (*d*) redissolving the precipitate and addition of ammonium sulfate to 25 per cent saturation, (*e*) dialysis of the supernatant solution to remove the ammonium sulfate and concentration, (*f*) addition of 'Merthiolate' (Sodium Ethyl Mercuri Thiosalicylate, Lilly) and passing the solution through a Seitz filter. The detail is considerably modified from our original method (Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran [5]).

Ten kilos of fresh pork kidneys are ground through a fine meat chopper (Tiffany's) into 15 liters of distilled water to which 300 gm. of sodium chloride and 300 c.c. of glacial acetic acid have been added. The vessel containing the mixture is stirred rapidly with a mechanical stirrer while the temperature is raised to 56° C. This temperature is reached in about 10 to 15 minutes and held there for 6 to 15 minutes, depending upon the appearance of a definite clumping of the inert protein.

To the clear filtrate, 632 gm. of ammonium sulfate per liter are added with stirring. The mixture is allowed to stand overnight at room temperature. The precipitate is then collected on Buchner funnels, No. 54 Whatman paper being used. The filtrate is discarded. The precipitate is dissolved in 2 liters of water, the ammonium sulfate content determined in an aliquot by direct nesslerization, and a total of 532 gm. of ammonium sulfate per liter is added with stirring. The precipitate which forms is collected on Buchner funnels, using No. 50 Whatman paper, a small amount of diatomaceous earth (hyflo-super-cel) being added to insure a clear filtrate. The filtrate is discarded. The precipitate is dissolved in 1.5 liters of water; the ammonium sulfate content of the solution is determined, and then a total of 190 gm. per liter of ammonium sulfate (25 per cent saturated) is added with stirring. The precipitate which forms is removed by gravity filtration in the cold through No. 5 Whatman paper and discarded. To the filtrate of the 25 per cent saturated precipitation 513 gm. of ammonium sulfate are added with stirring. The precipitate which is formed is collected on Buchner funnels, using No. 5 Whatman paper, diatomaceous earth being used as before. The precipitate is dissolved in a minimum amount of water and dialyzed overnight against running tap water (15° C. or below) and then against distilled water in cellophane sacs to remove the ammonium sulfate. Any precipitate of euglobulin which forms during the dialysis is removed and the extract concentrated in vacuo so that 1 c.c. of the material is equivalent to 100 to 170 gm. of original kidney.

The extract is centrifuged at high speed to remove any sediment which forms during the concentration. Sodium chloride is added to 0.8 per cent and the extract filtered through a Seitz filter. 'Merthiolate' may be added to it in a concentration of 1 : 5,000 after the extract is put through the Seitz filter. It is preferable to clarify the extracts before filtering through a Seitz filter by a preliminary filtration through a medium or fine Pyrex fritted filter.*

Extracts prepared in this manner lower blood pressure but are not free from pyrogens and materials which elicit shock-like reactions. Treatment of the final extract with 1 to 2 grams of kaolin per 250 grams of

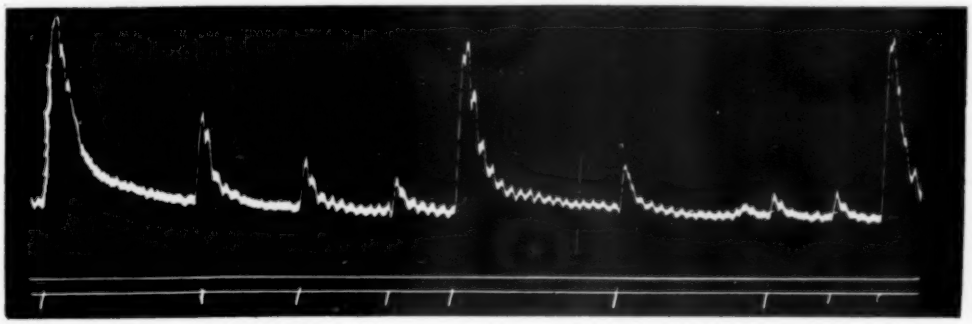

FIG. 1. The in vitro destruction of angiotonin by renal extracts as measured by pressor response produced by intravenous injections into a pithed cat:

Injection No. 1. Angiotonin 0.05 c.c. as control.
2, 3, 4. Injections of mixtures of a renal extract derived from 200, 400, 800 mg. of fresh kidney tissue and an equivalent amount of angiotonin, incubated for 30 minutes at 37° C. and then heated to 100° C. for 10 minutes.
5. Angiotonin 0.05 c.c.
6. Injection of another renal extract derived from 1000 mg. of kidney and the equivalent amount of angiotonin.
7, 8. Injections of a mixture of renal extract prepared from 800 mg. of kidney and the equivalent amount of angiotonin.
9. Angiotonin 0.05 c.c. control.

kidney at pH 4.0 while raising the temperature to 55° C. removes some of this material. This may be followed by reprecipitation with ammonium sulfate to 0.6 saturation. The final extract after dialysis should always be made isotonic before injection.

Assay of Potency. The assay of kidney extract in hypertensive rats and dogs is extremely time consuming and requires large amounts of material. Wide variations in response are observed in individual animals and this further complicates an already complicated problem. The need for a simpler test was apparent.

The following test must be considered as merely an experiment at the present stage (Helmer, Kohlstaedt and Page[6]). It is based on the pos-

* No. 10-358 in the Fisher Scientific Company catalogue.

sibility that angiotonin is the effector substance in hypertension; hence the ability of kidney extract to destroy angiotonin in vitro might be a measure of its antipressor activity.

One c.c. of extract equivalent to 12.5 to 100 mg. of original kidney is mixed with 1 c.c. of fiftieth molar buffer at the desired pH (4.0 or 7.0) and incubated at 37° C. for 30 minutes with 0.5 c.c. of standardized angiotonin solution. The reaction is halted by immersion of the tube in boiling water. The pressor response of an aliquot portion of the test solution is compared to that of untreated angiotonin by intravenous injection into pithed cats.

In order to compare readily the results of the assays the following index of angiotonin-destroying power was utilized:

$$\text{Angiotonin Index} = \frac{1}{\frac{\text{Pressor response in mm. Hg unknown}}{\text{Pressor response in mm. Hg standard}} \times \frac{\text{mg. kidney}}{100}}$$

Two Enzymes (Angiotonases) with Different pH Optima in Kidney Extract. Two enzymes with optimal ability to destroy angiotonin at approximately pH 4.0 and pH 7.5 respectively were found in our kidney extracts (table 1).

TABLE I

Effect of pH on Ability of Kidney Extract to Destroy Angiotonin

pH	Acid Stable Index	Alkaline Stable Index
4.0	0.69	0
5.0	0.55	0
6.0	0.50	1.38
7.0	0.34	4.00
7.5	—	5.88
8.0	0.28	2.94

We have attempted to correlate these results with those obtained from the tests on hypertensive rats. In calculating the *rat index* consideration was given to the amount of extract administered to lower the blood pressure in relation to body weight of the rat and the number of days required to lower the pressure. The index follows:

$$\text{Rat Index} = \frac{1000 \times (1, 2, 3 \text{ or } 4 \text{ anti-pressor action})}{\text{gm. kidney Kg. body weight} \times \sqrt{\text{days treated}}}$$

Grade 1, 2, 3 and 4 results are appraised as follows: Rats with systolic blood pressure averaging 180 to 200 mm. of mercury are used. Results are graded according to (1) the fall in blood pressure, (2) its duration, and (3) the presence or absence of signs of illness or reaction as evidenced by weight loss, hemorrhage, respiratory difficulty, etc. The fall and subsequent rise of pressure on discontinuing treatment must not be due to accidental occurrences such as may be associated with extremes of heat or cold nor due

to spontaneous changes in blood pressure which might occur in any one hypertensive animal.

Grade 1 is equivocal and not considered significant unless all animals on test follow the same course, or unless the animal had maintained a steady pressure above 200 mm. and shows a sustained fall below 170 mm.

Grade 2. A fall in pressure to between 140 mm. and 155 mm. or a well sustained fall below 160 mm.

Grade 3. A fall in pressure to from 130 to 140 mm. or a well sustained fall below 150 mm.

Grade 4. A fall in pressure below 130 mm. sustained at least two days.

The correlation between the two indices, especially when the angiotonin-destroying capacity is measured at pH 7.0, is reasonably good. It is our hope that this test in which in vitro destruction of angiotonin is employed will finally serve to replace those in which hypertensive rats and dogs are employed. Obviously, however, it must be established with certainty that angiotonin destruction and antipressor activity go hand in hand before the hypertensive animals as a test object can be abandoned. This has not as yet been accomplished.

Our animal and clinical results, however, suggest that the kidney extracts prepared to contain the enzyme with pH optimum at 7.0–7.5 is more active as an antipressor agent than the one with pH optimum at 4.0.

It must not be assumed that we necessarily consider the angiotonin destroying enzyme as identical with the antipressor substance in kidney extract. There is some evidence for this belief but it is insufficient to establish so important a point. We can only point out that we consider other possibilities as well worthy of investigation.

Antigenic and Shock-like Effects of Renal Extracts. As indicated last year, the occasional and unpredictable occurrence of severe reactions in which the blood pressure fell to shock levels shortly after administration of extract prevented their use outside a hospital. Although it is true that with increasing purity of the extracts the number of these reactions has markedly decreased, the fact that they remain unpredictable in their appearance necessitates further careful analysis of this problem. It has not been solved yet, but some of the difficulties appear to be in the process of solution.

As a means of testing the antigenicity of extracts the following method has now been in use for the past six months (Kempf and Page [7]). Antiserum was prepared in rabbits by injection of kidney extract which was known to produce reactions in patients. The rabbit antiserum was used to sensitize 250 to 275 gram guinea pigs by intraperitoneal injection (0.5 c.c.) Trial doses of kidney extract equivalent to from 5 to 10 grams of original kidney consistently killed such sensitized animals. As purification has proceeded, extracts have been prepared of which the equivalent of 40 to 60 grams of original kidney are required to kill the animal.

We have satisfied ourselves that renin purified in such a way as to be free of angiotonase is not the cause of the reactions.

Clinical Results

1. Effect on Arterial Blood Pressure. Despite the fact that extracts prepared in many different ways have been used in the treatment of our patients, reduction of blood pressure, especially the diastolic, has occurred in most. Some patients appear to have been resistant and showed no sig-

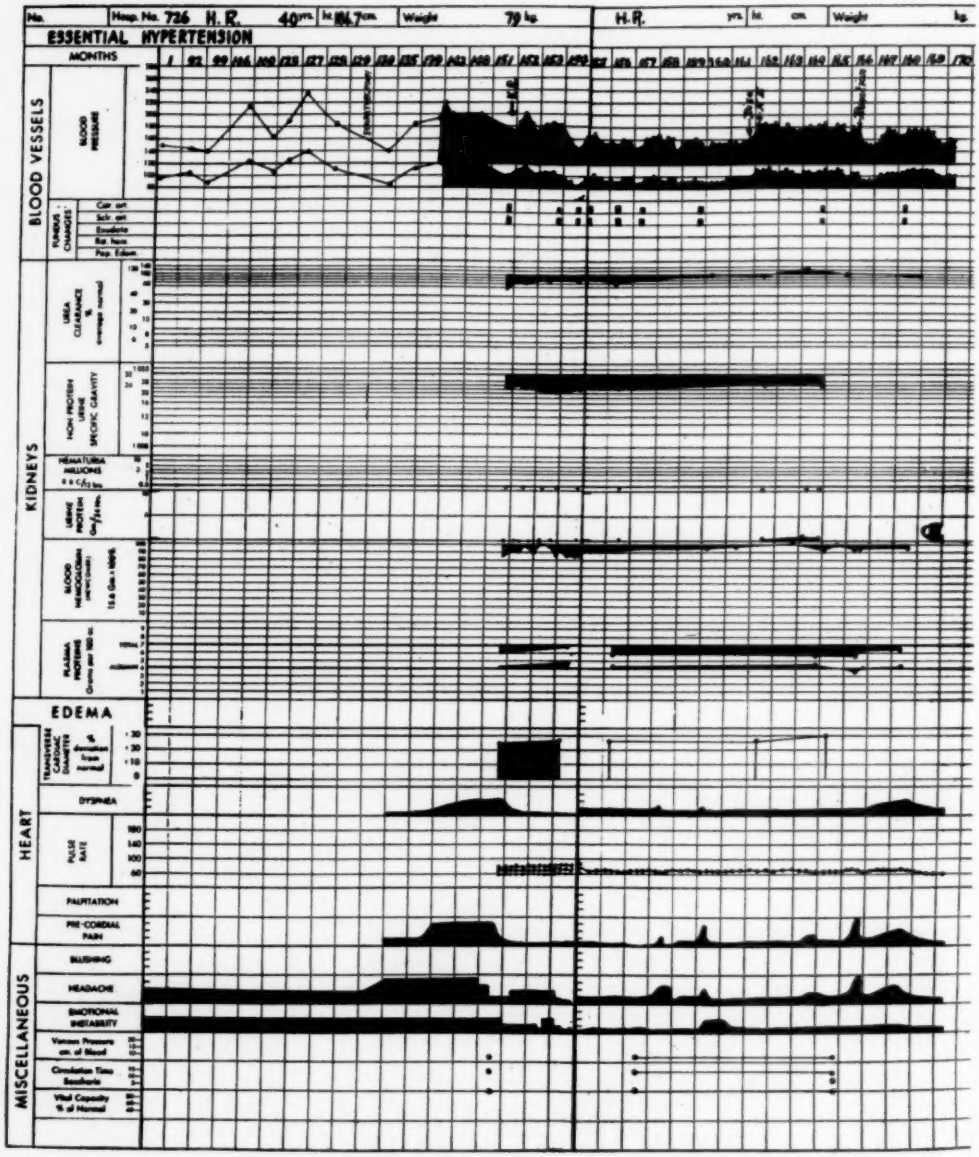

Fig. 2. Example of patient with essential hypertension treated with various types of kidney extract. Each dot under "blood pressure" represents the average of 7 daily blood pressure measurements.

nificant fall. This is a phenomenon we have also observed in dogs. Whether it is a quantitative problem so that more extract would have lowered the pressure, we do not know.

Fever as a sequel to injection of extract occurs much less frequently than during last year, and the local tissue response is also milder. Indeed, in a number of patients local reactions are insignificant. With reduction in the number and severity of reactions there has, however, been an associated loss of antipressor activity. In some patients it might be supposed that the entire antipressor action was due to reactions both local and general, but these seem to be the exceptions, not the rule. The usual result in patients is a fall in blood pressure associated with daily febrile response of one or two degrees for the first few days of treatment. After this initial period, no appreciable fever occurs. Injections are given daily, and if nothing untoward happens within three weeks the patient is discharged from the hospital to our out-patient clinic for further treatment.

2. Effect on Eyegrounds. Perhaps the most impressive single change caused by administration of kidney extract is its effect in reversing the morbid changes seen in the eyegrounds of patients suffering from the malignant syndrome. All patients with this syndrome, after a suitable period (usually four to eight weeks) of treatment, either were free of eyeground change or exhibited minimal signs of it. It has always come as a surprise to observe diminution or disappearance of white, "hard" exudates. Often they are very slow to resolve. We have repeatedly observed that reversal of the eyeground changes may occur before any marked fall in blood pressure occurs. Whatever its mechanism, the change is striking.

3. The Effect of Kidney Extract on Cardiac Output and Size. Contemporary evidence demonstrates that cardiac output is either normal or moderately decreased in hypertension. It may be presumed that cardiac output is maintained usually at normal levels because of cardiac enlargement.

Taylor and Page [8a] have employed the ballistocardiograph to ascertain the effect on cardiac output of reducing arterial pressure by means of kidney extract. In brief, it was found that in 15 patients with afebrile reduction in pressure from 174 mm. Hg, mean pressure, to 140 mm. Hg, cardiac output increased roughly 15 to 20 per cent. When extract was discontinued and arterial pressure rose, cardiac output decreased to its former level.

These results seem to be significant in the light of the fact that administration of angiotonin to normal persons leads to decrease in cardiac output and the conversion of a normal tracing to one with contours closely resembling those observed in hypertensives. After treatment with kidney extract, the normal contour of the tracing reappears.

It is interesting to compare the effects of other pressor agents such as tyramine and methylguanidine with angiotonin in normal human beings. The most striking facts which emerged were that tyramine and methylguanidine produce very severe and disagreeable signs and symptoms and ballistocardiographic tracings with contours quite different from those of

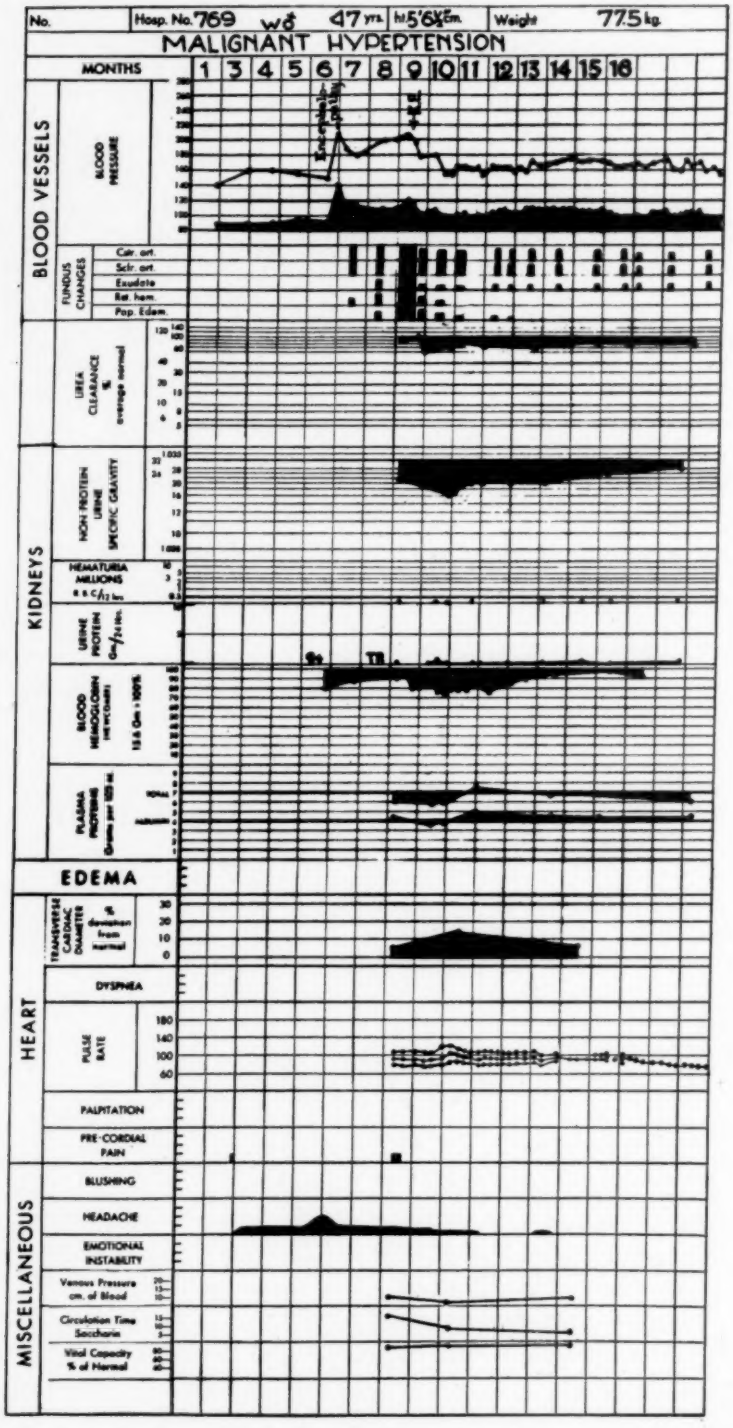

FIG. 3. Example of a patient with malignant hypertension treated with extract of sheep's kidney.

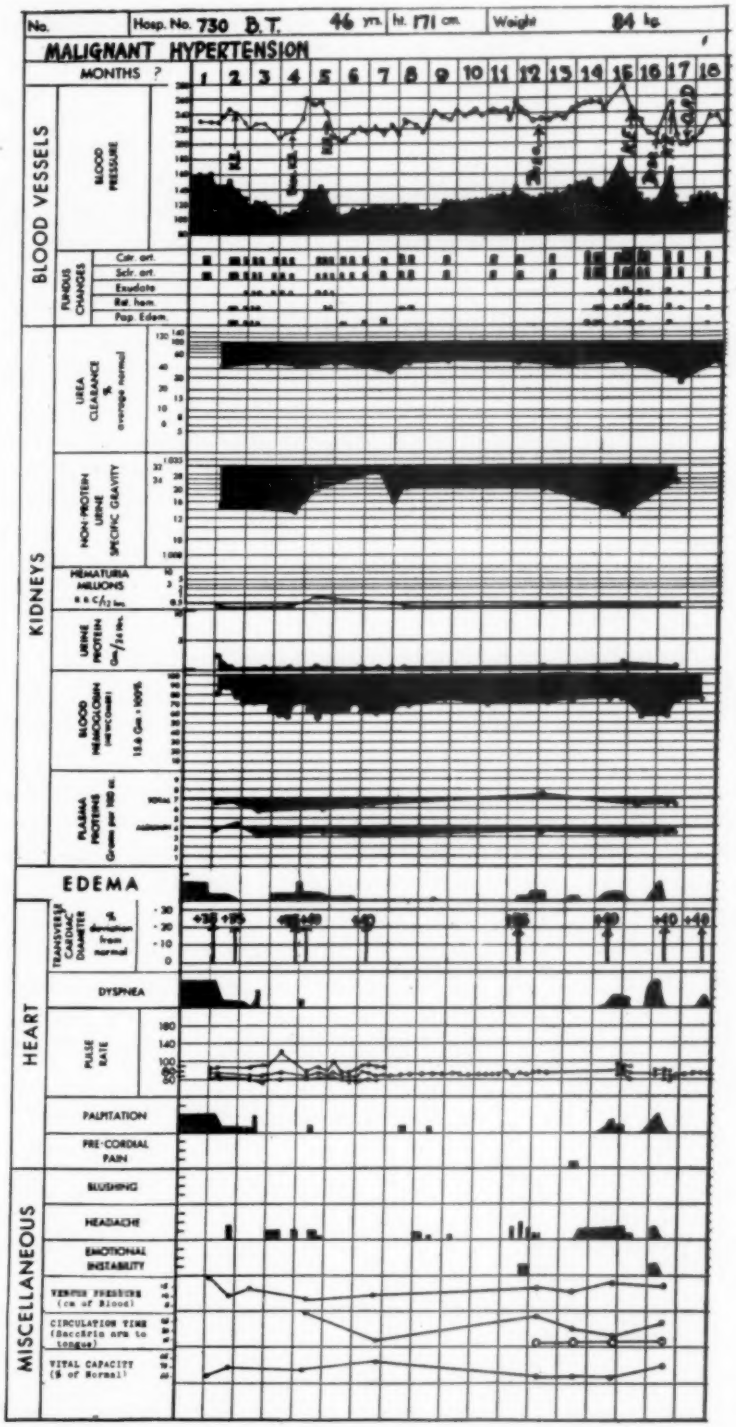

FIG. 4. Example of a patient with malignant hypertension treated at various times with different extracts of kidneys. Each time extract was discontinued the average blood pressure rose.

hypertensives. On the contrary, angiotonin elicits hypertension with little or no discomfort even when the appearance of the tracing is closely similar to that characteristic of patients with hypertension.

We have measured the size of the hearts of our hypertensive patients under treatment by means of roentgenograms, and from these calculated the percentage deviation from normal, using the Ungerleider-Clark tables. Occasionally decrease in size is observed but for the most part no change occurs even after a year or more. During the normal course of events without treatment, a significant increase would have been anticipated. It is our opinion that reduction in arterial pressure retards development of cardiac enlargement.

The changes in the electrocardiogram are interesting, especially the reversal of the T-waves from a downward to upright position. Of 17 patients with the malignant syndrome with T-waves inverted, 11 became upright after treatment and six showed no change. Ten patients with essential hypertension exhibited inverted T-wave and six of these became upright after treatment.

4. Effect on Kidneys. Apparently as the result of renal arteriolosclerosis or necrosis or both, patients suffering from hypertension nearly always show some impairment of functioning tubular secretory mass (Tm_D) and concentrating power (Corcoran and Page [8b]), and, in addition, the majority show evidence of ischemia of the residual tubular tissue. This ischemia of functioning tissue is apparently associated with constriction of the glomerular efferent arterioles (Goldring, Ranges, Chasis and Smith [9]). The renal functional changes of hypertension are, therefore, consistent with the view that they arise on the one hand from arteriolosclerosis, the result of increased arterial pressure (Wilson and Byrom [10]) and, on the other from the unopposed action of angiotonin (Corcoran and Page [11]).

The therapeutic action of renal extracts, if dependent upon the neutralization or destruction of angiotonin, would, from these premises, be exercised largely in decreasing the angiotonin-like intrarenal vasoconstriction and, because of the decrease of arterial pressure, in attenuating the progress of renal tissue destruction. Unequivocal demonstration of both of these actions is complicated by the fact that pyrogenic materials, such as unpurified inulin or typhoid vaccine, cause acute increases of renal blood flow due largely to efferent vasodilation (Chasis, Ranges, Goldring, and Smith [12]), and may, in addition, temporarily decrease arterial pressure in hypertensive patients. The measurements of renal functional changes during treatment with renal extracts were, therefore, made only in subjects whose temperature variations could be observed and the results obtained in recently (24 hours) febrile patients or dogs excluded from consideration. In normal and hypertensive dogs and in human beings suffering from essential hypertension the effect of treatment with renal extracts was, in every case, a decrease of glomerular efferent arteriolar tone and, in most instances, an

associated increase of functionally effective renal blood flow, i.e., changes consistent with inhibition of the renal action of angiotonin (Corcoran and Page [18]). No evidence of regeneration of tubular secretory mass (Tm_D) was obtained, but significantly, in nearly every instance, further loss of tubular tissue did not occur.

The interpretability of these observations has been increased by applications of formulae (Lamport [14]) dealing with renal hemodynamic changes in terms which permit comparison of data obtained in patients with varying levels of arterial pressure, anemia and plasma proteins. Briefly, in a group of 20 patients, 17 of whom suffered from malignant hypertension, the mean of systolic and diastolic arterial pressures decreased from 184 to 143 mm. Hg in observations made before and during treatment, whereas renal blood flow increased from 17 to 20.5 c.c. per minute per unit of functioning secretory tubular mass (Tm_D). The increase of renal blood flow during a *decrease* of arterial pressure denotes a decrease of calculated renal resistance of about 40 per cent. Perhaps significantly, efferent arteriolar resistance returned during treatment to levels which only slightly exceeded the normal, while afferent arteriolar resistance, although decreased, remained at a higher level. This residue of afferent arteriolar resistance may conceivably express structural changes in the afferent arterioles which remain unaffected by the inhibitor of angiotonin.

The changes in individual patients are of greater interest than the mean change, which was calculated without reference to the apparent effectiveness of the extracts in use at the time of observation. It should first be observed that in eight of 35 untreated patients there was no evidence of ischemia of the residual functioning tubular mass, an observation in accord with our demonstration of the absence of renal ischemia in the course of experimental renal hypertension (Corcoran and Page [15]). This maintenance of renal perfusion is apparently the result of equal increases of arterial pressure and renal resistance, whereas the presence of renal ischemia is associated with a disproportion in this balance. In view of the increase of cardiac output (Taylor and Page [8a]) which follows treatment with renal extracts and the resultant tendency to maintain arterial pressure at moderately increased levels, it is not surprising that in individual instances renal blood flow returned to or exceeded the normal rate in the presence of moderate residues of renal resistance. In three observations renal perfusion was shown to be decreased slightly during treatment, apparently as the result of decreased arterial pressure in the presence of fixed renal resistance.

Discussion

Results from other laboratories are now beginning to appear in the literature. Jensen, Corwin, Tolksdorf, Casey and Bauman [16] were able to prepare extracts which lowered arterial pressure in rats. Friedman, Jarman and Marrus [17] showed clearly that kidney extract reduced the blood

pressure of rats with cellophane perinephritic hypertension to normal, whereas other substances such as erythrol tetranitrate, garlic and parsley extract, etc., were ineffective. Zichis, Wald, Thomas and Barker [18] have proposed the hypothermic reaction observed in guinea pigs after injection of clinically active renal extracts as a rapid method of assay.

The process for the preparation of kidney extract has been altered from their original method by Grollman, Harrison and Williams.[19] Kidneys are dehydrated and dried preliminary to their extraction with acidulated water. They find the principle effective in lowering blood pressure in hypertensive rats is dialysable. When this material is concentrated it lowers the blood pressure of hypertensive rats when given by mouth just as they found their previous extracts active when given by mouth to patients. In their opinion results obtained by parenteral administration may be due merely to non-specific toxic impurities. Hence, their work is done by feeding the extracts by mouth. Their point is undoubtedly well taken. We, however, have had no experience with giving extracts by this route.

Almost nothing is known concerning the manner in which kidney extract lowers blood pressure. As discussed above, kidney extract is able to destroy angiotonin. Bing, Zucker and Perkins [20] found that the destruction did not occur by oxidative deamination since (a) oxygen is not necessary for the reaction, (b) destruction of angiotonin occurs without inactivation of hydroxytyramine, and (c) angiotonin is destroyed in the presence of octyl alcohol. Amine oxidase evidently is not the enzyme in the kidney which destroys angiotonin.

We have treated in the past two years, for longer or shorter periods, 37 patients of whom 24 suffered from the malignant syndrome and 13 with essential hypertension. Of the former, six died in uremia and three of cerebral hemorrhage, and of the latter none is dead. The most striking changes in the patients with the malignant syndrome were reversal of the eyeground changes with improvement of vision, changes of the inverted T-wave to an upright position, either moderate increase in renal blood flow or at least no decrease, increase in cardiac output and decrease in diastolic blood pressure. Although in the early stages pyrogenic reactions may at times have contributed to the fall in pressure, it appears doubtful that they are the main cause.

On the basis of contemporary knowledge there is reason to believe that the chief action of kidney extract is to oppose the action of angiotonin, but this certainly cannot be taken as established. It is at present a useful working hypothesis.

Both Murphy [21] and Barker [18] and their associates have prepared extracts which are active and have been used with some success in patients. Murphy [22] has treated 11 patients with malignant or premalignant hypertension. Seven of the patients responded satisfactorily, two were resistant, and two were symptomatically improved without a corresponding drop in blood pressure.

Summary

1. Improvement in preparation of kidney extracts has been made in that local and general reactions have been much reduced in number and severity. The yield of active material remains poor.

2. An in vitro assay method depending upon the ability of kidney extract to destroy angiotonin has been devised. There is suggestive evidence that a direct relationship exists between antipressor activity and ability to destroy angiotonin, but this has not been proved.

3. Two enzymes which destroy angiotonin (angiotonase) are contained in kidneys, one with optimal activity at about pH 4.0 and the other at about pH 7.5. The latter enzyme appears abundantly in the more active antipressor extracts.

4. A method for semiquantitative determination of the antigenic properties of kidney extract has been proposed depending upon the preparation of antiserum to a reaction-producing extract, sensitizing a guinea pig with it and ascertaining the amount of test extract required to kill the guinea pig.

5. Pyrogenic and local tissue reaction may contribute to the lowering of blood pressure in some patients but it appears unlikely to be the chief cause. It is suggested that part of the antipressor activity of kidney extract is due to its ability to neutralize angiotonin. This notion can be accepted only as a working hypothesis.

6. Kidney extract increases cardiac output in hypertensive patients when arterial pressure falls and tends to restore the contour of the ballistocardiographic curve from that usual in hypertension to normal.

7. In both hypertensive animals and man, kidney extract relaxed the efferent glomerular arteriole and this was associated in most instances with an increase of functionally effective renal blood flow, i.e., changes consistent with the inhibition of the renal action of angiotonin. No evidence of regeneration of secretory tubular cells was obtained but significantly in many cases further loss did not occur.

8. The clinical results on 37 patients of whom 24 had the malignant syndrome and 13 essential hypertension, and who have received a large variety of test lots of kidney extract, continue to be encouraging. Except for the lessening of reactions the clinical results are much the same as reported last year.

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ILEOSTOMY FOR CHRONIC ULCERATIVE COLITIS (END RESULTS AND COMPLICATIONS IN 185 CASES) *

By J. Arnold Bargen, M.D., F.A.C.P., Wallace W. Lindahl, M.D., Frank S. Ashburn, M.D., and John deJ. Pemberton, M.D.,
Rochester, Minnesota

The evolution of ileostomy as the foremost surgical procedure for the treatment of chronic ulcerative colitis of the thromboulcerative type has had a long and devious course. The long years during which it was being evaluated, as well as study of the cases in which it was done, brought to the fore sporadic attempts to substitute for it such maneuvers as appendicostomy, cecostomy, colostomy and ileosigmoidostomy. These operations were always eventually replaced by the seemingly inevitable ileostomy.

General Considerations

An attempt has been made to exercise fair and unbiased judgment on this surgical procedure by study of (1) end results for 185 patients who underwent this operation for chronic ulcerative colitis of the streptococcic type, (2) the reasons for which ileostomy was carried out and (3) the complications directly or indirectly attributable to ileostomy in such cases.

Final evaluation of any form of treatment for chronic disease must depend on prolonged observation of a fairly large group of patients. Our study included 185 patients operated on consecutively at the Mayo Clinic in the years from 1913 through 1939, or a period of 27 years. During this period 186 patients suffering from "chronic ulcerative colitis" underwent ileostomy at some time during the course of their disease. Of the entire group (186), only one patient was not traced postoperatively and this patient is not included in this study of 185 patients. The number of patients operated on each year is summarized in table 1.† It will be noted that the number of patients who underwent ileostomy varied greatly from year to year. During the early period (1913 to 1921) ileostomy was performed more frequently than during subsequent periods. During this early period one of the reasons for performance of ileostomy was the belief that ileosigmoidostomy could be performed safely at a later date, but this was soon proved to be unsatisfactory. Later, ileostomy became the first stage of a series of operations designed to remove the entire colon. The number of patients who received this type of treatment (colectomy) was limited by the high operative risk associated with it as well as by the fact that since some

* Read before the meeting of the American College of Physicians, St. Paul, Minnesota, April 23, 1942.

† Total in table 1 is 188 patients, but only 185 are concerned in this study. See footnotes to table 1 for explanation.

of the patients had obtained sufficient relief from ileostomy alone, the subsequent performance of colectomy was not thought to be advisable. The comparatively large number of cases in which ileostomy was carried out in the years 1917 to 1926, inclusive, is expressive of the lack of adequate medical management in those years. During that period, in many cases, ileostomy was performed early in the course of the disease, or it was performed for the

TABLE I

Number of Patients Undergoing Ileostomy, 27 Years

Year	Patients Undergoing Ileostomy	Total New Patients with Chronic Ulcerative Colitis Seen
1913	1	
1914	0	
1915	7	117
1916	8	
1917	15	
1918	9	38
1919	18	40
1920	12	42
1921	6*	50
1922	9	52
1923	16	57
1924	13	63
1925	8	102
1926	12†	134
1927	3	154
1928	5‡	189
1929	8	197
1930	2	202
1931	9	140
1932	1	110
1933	0	124
1934	6	165
1935	1	175
1936	2	
1937	8	
1938	4	1150§
1939	5	
Total	188	3301

* One patient operated on in 1921 not included in text of study because she was not traced postoperatively.

† One patient operated on in 1926 not included in text of study because at time of ileostomy he was found to have tuberculous enteritis with tuberculous peritonitis.

‡ One patient who came to clinic in 1928 had undergone ileostomy elsewhere, and was not included in text of study.

§ The figure 1150 is approximate but correct to plus or minus 10.

fulminating forms of the disease, with disastrous results. It was when we encountered patients who had the fulminating forms of chronic ulcerative colitis that we used to feel that when available medical measures did not seem to achieve success, ileostomy was to be undertaken as another therapeutic measure. We believe the mortality rates accompanying such a course speak for themselves. It was never a question of performance of ileostomy as a last resort, nor was the operation itself postponed until the

patient's condition was such as to make it a most dangerous procedure. The high mortality rate associated with ileostomy for this group of patients simply bespeaks the serious nature of this particular form of colitis and the inadequacy of all forms of therapy during the early years of the struggle for control of this devastating disease.

The reader should constantly keep in mind the fact that this paper is an analytic review of a form of treatment (ileostomy) carried out during a period of 27 years. All deaths, immediate as well as late, are included in our study. In no sense is the performance of ileostomy for any given group of patients to be considered as representing immature judgment, for in every instance it was undertaken after mature and detailed consideration, by clinicians and surgeons of wide experience, of all factors in a given case. We are attempting to present frankly and critically our experiences with this form of treatment.

In recent years ileostomy has been carried out more frequently for complications of "chronic ulcerative colitis" than for other reasons. Ileostomy has been employed at the Mayo Clinic as a form of treatment for chronic ulcerative colitis for approximately 5.5 per cent of the total number of patients suffering from "chronic ulcerative colitis" observed in those years.

Explanation of the Grouping System

Basic Plan. The 185 patients were divided into three groups in regard to indications for ileostomy.

Group 1. Group 1 included 86 patients who had undergone ileostomy because of chronic progressive and intractable symptoms of ulcerative colitis without necessarily severe exacerbations.

Group 2. Group 2 included 63 patients who had the severe and fulminating forms of chronic ulcerative colitis, with acute symptoms at the time of operation.

Group 3. Group 3 included 36 patients who were operated on primarily because of complications and sequelae of ulcerative colitis.

Table II

Complications Considered to Be Indications for Ileostomy in Chronic Ulcerative Colitis (36 Patients)*

Type	Number
Stricture, rectum or colon	11
Abdominal tumor, with proved or probable carcinoma	10
Incompetent anal sphincters	7
Extensive perirectal infection not responding to other treatment	7
Polyposis, colon	4
Perforation, colon	4
Massive hemorrhage, from colon	4
Intestinal obstruction	4
Total	51

* 51 complications occurred in 36 cases.

The complications considered to be indications for ileostomy in these 36 cases have been summarized in table 2, and a graphic explanation of the grouping system appears in table 3.

Survival According to Definite Periods. To study the records of patients from the standpoint of the length of their survival, they were divided into three periods as indicated in table 4. A more nearly accurate evaluation of the results of ileostomy was thus obtained, as well as information concerning the risk associated with the procedure. It will be noted that 35 patients lived less than 14 days after ileostomy, and that 20 patients lived more than 13 days but less than six months postoperatively. Members of the second

TABLE III

Grouping of Patients According to Indications for Ileostomy (185 Patients)

Group	Patients	Condition at Time Patient Seen
1	86	Chronic, progressive, intractable symptoms without severe exacerbations
2	63	Acute symptoms of fulminating disease at the time of operation
3	36	Complications of chronic ulcerative colitis

group would seem to represent those patients who were able to withstand ileostomy but died as the result of progression of ulcerative colitis in spite of the operation.

Thus, represented in period 3 (table 4) are 130 patients concerning whom a fair study of the effect of ileostomy could be made. Among these 130 patients a study of the incidence of recurrence of symptoms of colitis and the complications arising after ileostomy could be made, since a period of six months seems sufficient for the patient to adjust himself or herself to an ileac stoma. Also among these 130 patients, a fairly accurate appraisal of the end results of ileostomy as a method of treatment could be made. A summary of this study can be obtained by inspection of tables 3 and 4. The tables show that the mortality rate among those patients who underwent ileostomy

TABLE IV

Results of Ileostomy on Basis of Length of Survival after Operation (185 Patients)

Group	Period 1		Period 2		Period 3	
	Lived Less than 14 Days		Lived Less than 6 Months but More than 13 Days		Lived More than 6 Months	
	Number	Per Cent*	Number	Per Cent*	Number	Per Cent*
1	8	22.8	4	20.0	74	56.1
2	21	60.0	13	65.0	29	22.3
3	6	17.1	3	15.0	27	20.8
Total	35	18.9†	20	10.8†	130	70.3†

* Of total number of cases in each period.
† Of total number of cases in entire study.

TABLE V

Causes of Death: Patients of Period 1*
(35 Patients)

Death, Cause	Patients, Number
Peritonitis	14
Inanition and exhaustion	6
Bronchopneumonia	5
Perforation of colon, after ileostomy	3
Inability to control diarrhea from ileac stoma	2
Postoperative shock	2
Hemorrhage from colon, after ileostomy	1
Parotitis	1
Coronary occlusion	1
Total	35

* Died within 14 days after ileostomy.

while an acute exacerbation of the disease was present was roughly three times as great (except in period 3) as the mortality rate among those patients undergoing operation at a time when acute symptoms were not present or among those operated on because of complications or intractability of the disease.

An analysis of the causes of death of patients in period 1 appears in table 5; of deaths of patients in period 2, in table 6.

TABLE VI

Causes of Death: Patients of Period 2*
(20 Patients)

Death, Cause	Patients, Number
Peritonitis	6
Progression of ulcerative colitis	5
Inanition and exhaustion	3
Pulmonary embolism	2
Further operative procedures	1
Bronchopneumonia	1
Postoperative hemorrhage from colon, after ileostomy	1
Inability to control diarrhea from ileac stoma	1
Total	20

* Lived more than 13 days and less than 6 months after ileostomy.

ESSENTIAL NATURE OF THE STUDY: GENERAL RESULTS

Our study then concerns itself largely with the 130 patients who survived ileostomy for more than six months. The incidence and severity of the recurrence of symptoms of colitis after ileostomy were studied among the 130 patients who survived this period. It would seem that those patients who would respond to this form of therapy would have had sufficient time in which to adjust themselves to the changes which follow ileostomy. The

condition of the patients was graded on the basis of 1 to 4, depending upon the severity of the recurrence of symptoms of colitis (table 7). The condition of these 130 patients was influenced in several instances by the performance of other types of operations after ileostomy.

It is seen, then, that only 79 of the 185 patients derived real benefit from ileostomy. Of the 37 patients whose subsequent symptoms were of grade 1 (table 7), seven underwent other operations after ileostomy. Of the 42 patients whose subsequent symptoms were of grade 2 (table 7), 10 had further surgical treatment after ileostomy. The majority of patients who underwent further surgical treatment did so because of continued intractable symptoms of colitis. In most instances the beneficial result obtained could be attributed to the fact that another type of surgical procedure followed ileostomy. This additional surgical procedure included partial or total colectomy.

TABLE VII

Incidence and Grade of Recurrent Symptoms, 130 Patients of Period 3*

Grade	Explanation of Grade	Number
1	Symptom-free, or only mild recurrent symptoms; patients satisfied	37
2	Patients had frequent symptoms of colonic disease; but were satisfied (improvement)	42
3	Patients survived for considerable time, but severe and frequent recurrence (no improvement)	25
4	Severe and frequent recurrence; death within relatively short time (no benefit from ileostomy)	26

* Survived for more than 6 months after ileostomy.

It would appear, therefore, that the incidence of recurrence of infection in the colon after ileostomy is high. Fifty-one patients, or 39.2 per cent of those who survived ileostomy for six months or longer, had severe, frequent recurrences of the disease (table 7).

COMPLICATIONS WHICH FOLLOWED ILEOSTOMY

Prolapse of Ileum. Prolapse of a part of the ileum through the ileac stoma was the most common complication to arise after ileostomy. There were 27 such cases. Operative procedures performed for the correction of the prolapse resulted in the death of the patient postoperatively in four instances. One other patient died as a result of such prolapse; an operation to correct the prolapse had not been performed because the poor general condition of the patient would not permit it. This complication at times constituted the only noteworthy complaint of the patient, and was difficult to control without resort to additional surgical treatment.

Formation of Abscesses and Fistulae. Abscesses and fistulae occurred in 19 instances. The fistulae usually opened into the ileum from the abdominal wall at a point on the ileum proximal to the ileac stoma. Blood, pus and fecal material drained from the fistulous openings in variable

amounts. An abscess appearing in the abdominal wall was usually the first sign of a latent fistula. Systemic reactions in the form of chills, fever, anorexia, weakness and loss of weight occurred in the course of fistula formation. Not infrequently a single patient had several abscesses within the abdominal wall. Involvement of the distal portion of the ileum by the disease process may have been a predisposing factor to the formation of abscesses and fistulae.

Intestinal Obstruction. In 13 patients intestinal obstruction developed subsequent to ileostomy. Five of these patients died soon after the operation that was performed for correction of the obstruction. The poor physical condition of the patient before the onset of intestinal obstruction seemed to be a potent factor in the high mortality rate which followed surgical intervention for correction of the obstruction. The relative frequency and the high associated mortality rate of this condition depict its serious nature.

Chronic Infectious Arthritis. Sixteen patients had recurrent episodes of a chronic infectious type of arthritis after ileostomy. Several patients returned to the clinic subsequent to ileostomy primarily because of this condition. All the patients suffering from arthritis had recurrent infection in the colon. Other infectious complications such as perirectal infection, abscess of the abdominal wall and formation of fistulae, pyoderma and infection of the urinary tract were frequent among these patients. In the majority of these patients no exact sequence between exacerbations of the infection in the colon and exacerbations of the arthritis could be determined. One patient who had severe recurrent exacerbations of arthritis obtained complete relief after colectomy. This patient has been entirely well (at the time of this report) for nine years after colectomy. Patients who had had arthritis before the performance of ileostomy did not appear to obtain relief from the operation. It is to be noted that among 11 of the 16 patients the first symptoms of arthritis appeared after the performance of ileostomy.

Stricture of the Rectum, Colon or Stoma. Stricture of the rectum, of the colon, or at the ileac stoma occurred among 10 patients to a severe degree, but developed in a milder form in many others. In such cases purulent material drained freely from the rectum for variable periods, when suddenly, without other symptoms, drainage would subside or cease entirely and fever, chills, anorexia, abdominal pain and tenderness would occur. Surgical drainage of the colon was found necessary in some of these cases. In two cases stricture of the ileac stoma developed which was of sufficient degree to necessitate surgical intervention for relief.

Polyposis of the Colon. In 13 patients polyposis of the colon occurred after the making of the ileac stoma.

Perirectal Infection. Perirectal infection in the form of perirectal abscess, rectovaginal fistula or fistula-in-ano developed among nine patients after ileostomy. Twenty-four other patients had had this difficulty prior to ileostomy. Fourteen of these 24 patients seemed to have derived benefit

from ileostomy. In 22 of the 24 patients the perirectal infection was considered to be one of the indications for ileostomy. The results would suggest that ileostomy was a helpful form of treatment for these particular patients.

Urinary Complications. Urinary complications occurred among 16 patients. Four patients had chronic glomerular nephritis. In six cases renal stones developed and in two others typical histories of renal colic had been obtained. In three urethrorectal fistulae developed. Of these three patients two died within 14 months after ileostomy. One of these died as a result of carcinoma of the gall-bladder with metastatic lesions, and the other died of inanition associated with further exacerbations of the colitis. The third patient was alive seven years after ileostomy and during these years no improvement had occurred as to the condition of the fistula. One patient suffered from recurrent attacks of cystitis.

Carcinoma. In six patients carcinoma developed subsequent to ileostomy. In three the carcinoma occurred in the rectum, in one in the gall-bladder, in one in the ovary, and one patient died of generalized abdominal carcinomatosis of undetermined origin.

Cutaneous Lesions. Five patients complained of recurrent cutaneous lesions. Three of these had pyoderma gangraenosum, one erythema nodosum and one dermatitis about the iliac stoma. One of the patients who had suffered from pyoderma with each exacerbation of colitis prior to ileostomy had the same complication after ileostomy.

Hemorrhage. In nine cases hemorrhage was a prominent symptom. In four of the nine cases hemorrhage was so severe that it was thought advisable to perform further surgery in order to save the patient's life. Three of these four patients died postoperatively. In two other patients the hemorrhage was so severe that it was thought to be the major factor contributing to the early death of these patients. In this group of nine cases severe rectal hemorrhage had been a prominent symptom prior to ileostomy. This would suggest that ileostomy had but little beneficial effect on the patients who had severe rectal bleeding. It is worth noting that only four patients of our entire group underwent ileostomy because of severe hemorrhage, whereas nine suffered severely from hemorrhage after ileostomy. Cave[4, 5, 6] has pointed out that "massive hemorrhage" should not be accepted as an indication for ileostomy. Garlock and others, however, have considered it to be a major indication for ileostomy.

Anemia. A hemoglobin-deficiency type of anemia was present preoperatively in all but seven of the cases studied. The average preoperative value for hemoglobin of a large group of these patients was 60 per cent of normal. In a similar group studies carried out several months to years after ileostomy disclosed that the average value for hemoglobin was 64 per cent of normal. Continued anemia was traced in most instances to continuation of the infective process in the colon.

Miscellaneous Complications. Other serious sequelae occurring among patients who had ileac stomata included leukemia, multiple sclerosis in one, cirrhosis of the liver in one, severe corneal ulcer with conjunctivitis in one, pulmonary tuberculosis in one, recurrent cholecystitis in one, and bronchiectasis in one. In two patients an ileocecal granuloma developed. Some, at least, of these lesions, may have occurred because of the infective process in the colon.*

The fact that some patients may experience serious difficulty merely because ileostomy has been performed would in itself seem to discredit the suggestion of some [4, 7, 13] that ileostomy should be carried out early in the course of the disease.

Patients Who Survived Ileostomy more than Fifteen Years

In an effort to determine what sort of patient would derive most benefit from ileostomy, a study was made of 18 patients who were known to be living 15 years after ileostomy. The period of observation after ileostomy in these cases ranged from 15 to 24 years. The average follow-up period was 19 years. Ten patients were females and eight were males. The average age of these patients at the time of performance of ileostomy was 32 years. The average duration of symptoms of chronic ulcerative colitis prior to ileostomy was four and a half years, but in individual cases the duration varied from one to 15 years. Thirteen patients underwent ileostomy because they had had intractable symptoms, but without severe exacerbations. Four patients were operated upon for an acute exacerbation of the disease; one for rectal stricture and persistent symptoms of perirectal infection. Seven of the 18 patients had undergone colectomy after ileostomy. Two of these seven patients had undergone total colectomy with removal of the rectum; five had undergone subtotal colectomy; that is, removal of the large intestine as far as the rectosigmoid junction.

Several factors seemed to be responsible for the satisfactory results obtained for this small group of patients: (1) the majority of these patients had had the disease for a relatively short time, (2) the patients were young adults and thus were able to adjust their lives to the handicaps imposed by the performance of ileostomy, (3) most of the patients were operated on for chronic intractable symptoms and not acute exacerbations of the disease and (4) the survival after colectomy in itself removed the opportunity for any further development or existence of colonic disease in seven of the 18 patients.

Colectomy after Ileostomy

A portion or all of the colon was removed from 30 patients of the entire group subsequent to the performance of ileostomy. In 18 instances the entire colon was removed to as far as the rectosigmoid region. In five cases

* The number of complications in this section exceeds the number of patients because some patients had more than one complication.

the cecum, ascending portion of the colon, and a portion of the transverse colon were removed; in four the entire colon, including the rectum, was removed. From two patients the terminal portion of the ileum, the cecum, ascending part of the colon and a portion of the transverse colon were removed, with the performance of ileosigmoidostomy at the time of removal of the colon. One patient underwent abdominoperineal resection of the rectum for carcinoma. Of the 30 patients operated on in this particular group, 11 died during the immediate postoperative period.

It might be assumed on the basis of the foregoing that the risk of colectomy is prohibitive, but it should be remembered that operations in this group were performed in the years from 1913 to 1940. Moreover, as more experience has accrued in the selection of patients for colectomy and in the proper choice of the time at which to do colectomy in individual cases, and as marked advances have been made in preoperative and postoperative

TABLE VIII

Colectomy after Ileostomy: Type of Operation, Deaths (30 Patients)

Operation	Number	Died Postoperatively
Total colectomy with removal of the rectum*	4	0
Colectomy including the entire colon to the rectosigmoid*	18	7
Resection of cecum, ascending colon, a part of the transverse colon and the terminal ileum	5	3
Resection of cecum, ascending colon and a part of the transverse colon with ileosigmoidostomy	2	0
Abdominoperineal resection	1	1
Total	30	11

* In these cases, in most instances, removal of the bowel was accomplished by multiple operations.

care, the mortality rates accompanying this operation have been greatly reduced. This statement is in general agreement with the views of others of more recent experience.[2, 3, 4, 5, 6, 8, 9, 10] In well-selected cases colectomy will be not only the treatment of choice but also the only satisfactory treatment. Ten of the 18 patients from whom the colon was removed to as far as the rectosigmoid and four who underwent removal of the entire large intestine were in good health for from two to 20 years after such removal. Data concerning the 30 patients in this group are presented in table 8.

ILEOCOLOSTOMY

In 20 cases ileostomy was followed by ileocolostomy and subsequent closure of the ileac stoma. In seven of these cases the patient's symptoms were completely relieved. The average follow-up period in these cases was six years. The nature of the colitis in these cases is not clear, but as a review of the records was made, necessarily years later, the impression was gained that in some of the earlier of the 20 cases, at least, the colitis may not

have been of the streptococcic type. In two of them, however, the patients seemed to be well and had remained so to the time of this report. Five of the patients were operated on in the years 1915 and 1916. During this time roentgenologic investigation of the colon was not nearly so accurate as it is today. Nine of the 20 patients had a recurrence of colitis within a short period after ileocolostomy. Four of the patients who had a recurrence of colitis died within 12 years after operation. One patient was alive 20 years after ileocolostomy, in spite of recurrent symptoms. Four of the 20 patients died of postoperative complications.

It can be seen, then, that eight of the 20 patients in this particular group were dead within 12 years after operation. Five other patients were known to be alive within this period, but with a recurrence of colitis during a subsequent period of observation averaging eight years. Seven other patients were completely relieved of their symptoms during a period of observation averaging six years.

Because of the poor results obtained from ileosigmoidostomy for ulcerative colitis, the operation has been attempted after ileostomy only six times since 1921. The reason for this is that prior to consideration of ileosigmoidostomy, patients have been carefully examined for any signs of active inflammation in the colon, and if such signs are encountered, the patient concerned is not considered to be suitable for the operation. The mortality rate and the recurrence of colitis both are high when the operation necessitates cutting through an actively diseased portion of bowel.

Ileostomy for Patients Who Have Undergone Previous Operations

Twelve of the patients included in this study had undergone surgical treatment other than ileostomy before they came to the Mayo Clinic. Four had undergone appendicostomy, four had undergone colostomy, two had undergone ileosigmoidostomy (one with exclusion of the colon) and two had undergone cecostomy. In only two instances had the previous surgical procedure resulted in temporary satisfactory improvement. In these two instances the continuity of the bowel was reëstablished and colitis subsequently recurred. Ileostomy was performed for each of these patients later. Nine patients survived ileostomy and three died in the immediate postoperative period. In each of the nine patients who survived ileostomy immediate improvement was noted. In the majority of these 12 cases the patients volunteered the information that they were more satisfied, as the result of ileostomy, than they had been after the previous type of operation. Among those patients who had previously undergone appendicostomy the stoma functioned poorly. There was a tendency for the colitis to recur either in the distal or proximal portions of the colon. One patient who underwent ileosigmoidostomy with isolation of the right portion of the colon had a recurrence of colitis in the isolated loop of bowel.

Comment

For patients who have "chronic ulcerative colitis" ileostomy is the only method of diverting the fecal stream which is practicable and which is at least reasonably satisfactory. The favorable immediate response to ileostomy of patients who have ulcerative colitis may be striking. Patients who survive the operation may gain weight and improve in general strength, so that during the immediate postoperative period the result might appear to be favorable. We thought it important, however, to study the courses of patients for a longer period than the immediate postoperative period. It is obvious that the immediate response is not of great interest because "chronic ulcerative colitis" is a disease in which remission can be obtained with the aid of other forms of therapy. The real concern is, therefore, whether or not patients are permanently benefited by the performance of ileostomy. Ileostomy for "chronic ulcerative colitis" has been discussed frequently and at length in recent years. Its value cannot be determined in a few weeks or months after it has been performed.

The procedure of early surgical intervention for "chronic ulcerative colitis," such as performance of ileostomy when minimal symptoms are at hand, has been much discussed. No one who has had much experience with this disease would subscribe to such a plan of attack. It is suggested, we believe, in the hope that after the disease has been healed the ileac stoma can be closed. In the first place, however, we wish to reëmphasize our belief that "ileostomy does not cure the disease." Moreover, it should be remembered that not only does ileostomy not cure, but that the disease often actually progresses rapidly after the performance of ileostomy. Consequently, few closures will ever be attempted, and this would imply that after ileostomy has been carried out, colectomy will become advisable. Surely no one can or would advise colectomy for a patient who has colitis which is in an early stage. Thus, the return to our original premise seems inevitable: ileostomy should be reserved for those patients who have complications and for the occasional patient who has intractable ulcerative colitis. It is unthinkable that surgical intervention can or ever will replace any well-planned medical regimen, in so far as "chronic ulcerative colitis" is concerned. Conversely, it is just as inadvisable to continue the medical management of patients who have complications demanding surgical treatment. This has been well pointed out by Rosser, Dixon and others.

There is a certain group of patients who have ulcerative colitis complicated by rather severe symptoms of perirectal infection and who usually are not helped by ileostomy, but who, rather, suffer as intensely from recurrent infection after ileostomy as they did previous to the operation. It may be that it is wise to operate reasonably early for this complication. The answer to this question has not been determined, for many patients with "chronic ulcerative colitis" complicated by perirectal abscess treated medically

have been restored to normal health and the fistula, if it has not healed, has been operated on successfully later.

In one case a blind loop of colon resulted because colostomy and later ileostomy were performed. This loop was left open for purposes of irrigation. Eventually, the open ends of this portion of colon were closed. Later, an exacerbation of infection in the isolated loop of colon occurred, and surgical drainage of this obstructed loop was necessary.

In one case of the acute fulminating form of ulcerative colitis colostomy was performed and then ileostomy was carried out, but the patient died of a progressive type of toxemia. This illustrates again the futility of surgical intervention in this form of the disease.

So-called single-barrel ileostomy was performed for one patient, and the distal segment of ileum was turned into the cecum. Stricture of the colon subsequently developed, and it was necessary surgically to drain the purulent material that had collected in the colon.

The mental reactions of these patients toward their ileac stoma were carefully observed when they returned to the clinic for observation postoperatively. Many patients had received the impression that the operation had been meant to cure them of their disease. Consequently, patients often returned clamoring for closure of their ileac stoma. Common reasons for this request were: freedom from symptoms, inability of patients to adjust themselves to the ileac stoma, a belief that they could not carry on social activities as they had before ileostomy, contemplation of marriage and, in some cases, the fact that patients had been told that closure might be hoped for after the symptoms of colitis had subsided. In the great majority of cases a badly scarred and contracted colon remained, and the possibility of a recurrence of infection was at hand at the time the patients returned for reëxamination. For this reason the continuity of the bowel was only very rarely restored.

Study of the records of patients who died soon after ileostomy impresses the investigator with the fact that when severe symptoms are present, such patients are very poor surgical risks.

Results of the studies carried out for this review would suggest that if and when the condition of a patient suffering from ulcerative colitis reaches the stage in which ileostomy seems to be advisable or necessary, the performance of colectomy subsequent to ileostomy should be seriously considered.

The fact should be kept in mind that this study is an analysis of a single measure of therapy for one of the most devastating afflictions which can attack the human body, and that the failure of ileostomy in individual cases never should be ascribed to improper application of the operation, but rather to the intractable nature of the malady for which it was attempted.

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PROPHYLACTIC AND THERAPEUTIC DETOXICATION

GUANIDINE, INDOLE AND HISTAMINE*

By Gustav J. Martin, E. H. Rennebaum, and Marvin R. Thompson,
New York, N. Y.

Introduction

Indole, histamine and guanidine are representative examples of toxic chemicals produced endogenously. These compounds were considered as a group not only because of their endogenous origin but also because each is associated with diseases known to afflict the human body. No study of therapeutic and prophylactic detoxication would be complete without a consideration of these toxic metabolites. It is to be emphasized that each is a representative of a group of toxic substances and that there is a large number of additional groups of toxic metabolites.

Histamine is formed through the action of putrefactive bacteria on histidine.[1] It has been shown that a bacillus is present in the intestinal contents which is capable of decarboxylating histidine. Hanke and Koessler,[2] in an examination of 26 human stools, found 16 to contain such a microorganism. Histamine has been isolated from intestinal contents as well as from loops of the large and small intestine. Hanke and Koessler found 500 to 600 grams of feces from normal individuals to contain 6 mg. to 20 mg. of histamine. When injected intravenously, histamine is toxic, even in small amounts, producing a condition simulating traumatic or surgical shock. When given by mouth, however, it is relatively inert, large amounts being tolerated. The histamine is destroyed by an enzyme, histaminase, described by Best.[3] It has been suggested that histaminase of intestinal mucosa serves as a protection against the small amounts of histamine which normally might be formed. It is an open question whether or not histamine formed in intestinal putrefaction can be a factor in systemic intoxications. Other members of this group are the ptomaines: cadaverine formed from lysine and putresine formed from arginine.

The toxemic theory of shock, a controversial issue, must be considered. Cannon[4] seemed to have placed the toxemic theory upon a logical basis, but more recently Blalock and his associates[5] have seriously questioned it. The most recent work of Moon and Kennedy[6] demonstrates the possibility of a toxic factor playing a causative rôle in certain instances in shock. In anaphylactic shock, in contrast to the secondary shock mentioned above, histamine is on a more firm basis as an etiological factor. Asthmatic at-

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tacks may be caused by histamine liberation into the blood stream. The severe though brief headache which follows the intravenous administration of histamine can be cited in support of possible involvement of this compound in headaches of the vascular type. Spriggs [7] suggests that migraine headaches are due to liberation of histamine with consequent vasodilatation and localized edema.

Immunity of the body to autointoxication applies only to the large intestine; an autointoxication from the small intestine is probable.

The abrupt fall of systemic blood pressure which results when noncoagulant venoms are injected intravenously results in a large part from the action of phosphatidase by the formation of lysolecithin and the liberation of histamine. Arthus [8] studied this hypotensive effect and noted its resemblance to that occurring in acute anaphylaxis in the rabbit and dog.

Feldberg and Kellaway [9] found that the injection of the venom of *Crotalus atrox,* of *Denisonia superba* or of the Indian cobra into the pulmonary artery of the perfused guinea pig's lung caused the appearance of histamine and coagulable protein in the venous perfusate. The effect of the intravenous administration of venoms can be largely explained on a basis of histamine liberation.

Thus, the probable involvement of histamine or related substances in surgical shock, anaphylactic shock, headaches, asthma, snakebite and other conditions has been established or indicated. It is, therefore, obvious that any means of altering the toxicity of histamine endogenously is important.

Indole is a product of intestinal putrefaction which affects the aromatic amino acids. The disagreeable and characteristic odor of feces is said to be due partly to two compounds, namely indole and skatole. Indole is oxidized and conjugated with the sulfuric acid radical to form indican.

Indole when given to the human subject by mouth causes dizziness and headache. Toxic doses of this substance are prevented from entering the systemic circulation by the barrier of the gut wall or through the detoxicating action of the liver. It is a known fact that certain individuals excrete large quantities of indican in the urine, which is indicative of excessive intestinal putrefaction.

Guanidine is another product of intestinal putrefaction believed to be involved in many physiological disturbances. It is a normal product of creatine metabolism, and when injected into animals in large amounts causes a rise in blood pressure. It was claimed by Major and his associates [10] that retention of this metabolite as evidenced by a rise in its concentration in the blood and reduced excretion in the urine could be demonstrated in hypertension. This theory has not been generally substantiated. Guanidine may play a minor rôle in parathyroid tetany, although it certainly is not the major factor. As recently as 1939, Major et al.[11] reported an increase in guanidine in the blood in experimental renal insufficiency which occurs both with and without accompanying hypertension. The compound may be an anhydride

of guanidine, glycocyamidine. It has been suggested [12] that guanidine intoxication is a significant factor in trichinosis. Dodd et al.[13] report that the concentration of guanidine in the blood increases in intestinal intoxication of infancy. The outstanding symptoms of alimentary toxicosis in infancy and early childhood are intensive vomiting and diarrhea, resulting in dehydration, acidosis and circulatory collapse. Mason et al.[14] note that guanidine occurs in blood in traces, but it is present in increased amounts in renal insufficiency and particularly in uremia. Some of the symptoms of uremia are duplicated in experimental guanidine poisoning. In both conditions vomiting, diarrhea, gastroenteritis, muscular twitchings, increase in blood pressure and respiratory disturbances are prominent, and, in advanced stages, apathy, stupor and circulatory collapse. Guanidine appears to be a physiological antagonist of calcium, the latter inhibiting the action of guanidine on the neuromuscular apparatus. In uremia, muscular twitchings may occur even when there is no central calcium deficit. In such instances the effect is attributed by these workers to the action of guanidine. In those cases in which a calcium deficit does exist, the muscular twitchings are more severe, presumably because there is insufficient calcium ion acting on the central nervous system to oppose adequately the effects of guanidine.

In addition to the above, other compounds of intensely toxic character are formed in the large intestine as a result of the decomposition of protein by the normal bacterial flora. Among such putrefactive products are phenol, cresol, skatole, ethylamine, isoethylamine, tyramine, etc. The body, through the detoxication mechanisms of the liver, can usually handle these toxic materials, but innumerable clinical conditions exist in which these detoxication mechanisms are not normal, and in which these toxic materials accumulate in the blood stream and tissues. In these conditions, it would obviously be desirable to speed up or facilitate the detoxication of these compounds, and it has been the objective of this work to attempt to influence the processes of detoxication by the administration of detoxifying compounds.

Experimental Technic and Results

White mice, 18 to 24 grams in weight, were used throughout these experiments. Acute toxicities were studied in approximately 5,000 mice. Indican excretions were studied in a series of 10 dogs. With each of the three compounds considered the oral or subcutaneous L. D. 50 was checked. It was evident from the outset that a multiplicity of factors affected the value, e.g., the suspending agent used, the osmotic pressure of solutions administered orally, the diet of the mice before use, the hydrogen ion concentration of the solutions, weight of mice and the usual biological variation. Each of the controllable factors received appropriate attention in all protocols throughout the study.

All compounds used by the body in detoxication were regarded as potential detoxifying agents for these physiologically important compounds.

Included among these compounds were cysteine, glycine, glutamine, sulfates, acetates and calcium glucuronate. A large number of other compounds of similar or unrelated structure were tried as potential detoxifying agents. In each instance in which a set of experiments included cysteine, the other sulfur-containing amino acids were also tried, namely, cystine and methionine. Frequently, the sulfur of these compounds is finally utilized in the form of sulfate, and, therefore, sodium sulfate was used to check its possible detoxifying effect. Glycine was replaced by alanine, serine, leucine, isoleucine and valine. Glucuronic acid was replaced by gluconic, 2-ketogluconic, galacturonic, mucic, saccharic, arabinic, pectic, lactic, pyruvic, glyoxallic acids. Dihydroxyacetone and all of the aldohexoses were also tried.

Acetic acid as its sodium salt, acetaldehyde, sodium lactate and sodium propionate were all tested for efficacy in supplying the acetyl radical. Xanthine, adenine and guanine were tested as representatives of the purine detoxifying action suggested by Neale and Winter.[15] No substitutes for glutamine were tried as none was known that might function as detoxifying agent. Its precursor, glutamic acid, however, was tested. Nicotinic acid, thiamine and a liquid yeast concentrate were tried, as reports[16] have appeared in the literature suggesting possible detoxifying effect. Lecithin, cephalin and cholesterol were tried as positive detoxifying substances. Choline was included as a contributor of labile methyl radicals.

In the early experiments, gum arabic in 10 per cent concentration was used as a suspending agent, but frequent unexplainable variations in control toxicity determinations led us to abandon gum arabic in favor of gum tragacanth at 0.5 per cent. Gum arabic, the crude material, occurs in every state of partial hydrolysis; and as one of the products of the hydrolysis of gum arabic is glucuronic acid, a detoxifying substance, we abandoned the use of this material entirely. The use of several control sets in each experimental group even in our earlier experiments prevented any misinterpretation of results. Volumes of material for oral administration were held below 0.8 c.c. In some studies the toxic material and the detoxifying chemical or chemicals were given in the same solution. In others the toxic material was given subcutaneously and the detoxifying substances were given orally. Oral administrations were made with a long blunt syringe needle and a tuberculin syringe graduated in 0.01 c.c. No group of animals less than 25 in number was considered, and no greater variations in weight than 4 to 6 grams in any set of 250 were permitted. The dietary régime of the mice before use was controlled by maintaining them on a stock ration for several days before use and then placing the mice on an unpolished rice ration for three days before use. This latter diet is a maintenance ration, calorically adequate but inadequate nutritionally for other than maintenance. Diet before use is a most important factor. Diet variation can cause experimental results to vary by as much as 50 per cent. This is a factor which has been all too frequently neglected in a consideration of control factors in acute toxicity experiments.

TABLE I

Action of Various Physiological Detoxifying Agents and Combinations of These Agents against Acutely Toxic Dosage of Guanidine, Indole or Histamine

Compound	Detoxifying Action with Guanidine	Detoxifying Action with Indole	Detoxifying Action with Histamine
Cysteine	+	+	±
Cystine	+	+	±
Methionine	++	+	±
Glycine	+	±	−
Alanine	−	−	−
Serine	−	−	−
Leucine	−	−	−
Isoleucine	−	−	−
Valine	−	−	−
Glutamic	−	−	−
Glucuronic	+	++	+
Gluconic	±	−	−
2-ketogluconic	−	−	−
Galacturonic	±	−	−
Mucic	−	−	−
Saccharic	−	−	−
Arabinic	−	−	−
Pectic	−	−	−
Lactic	−	−	−
Pyruvic	−	−	−
Glyoxallic	−	−	−
Dihydroxyacetone	−	−	−
Acetic	−	−	−
Acetaldehyde	−	−	−
Lactic	−	−	−
Propionic	−	−	−
Aldohexoses	−	−	−
Lecithin	±	−	−
Cholesterol	−	−	−
Cephalin	−	−	−
Guanine	−	−	−
Adenine	−	−	−
Xanthine	−	−	−
Nicotinic	++	−	−
Thiamine	−	−	−
Liquid Yeast	−	−	−
Ascorbic Acid	+	±	+
Glutamine	−	−	−
Choline	++	+	−
Sulfates	−	−	−
Ornithine	−	−	−
Aldobionic	±	±	±
Saccharolactone	−	−	−
Isoascorbic	±	±	−
Glucuronic Ferrous Chloride	+ −	+ −	−
Cystine Glycine Glucuronic Ascorbic	++	++	++
Cysteine Glutamic Glycine Ascorbic Glucuronic	+	+	+
Glycine Cystine Glucuronic Ascorbic Nicotinic	+++	++	+
Cystine Glycine Glucuronic Ascorbic Choline	+++	++	++

Table 1 presents a summary of the results obtained with various compounds and combinations of compounds in detoxifying histamine, guanidine and indole.

A consideration of table 1 clearly indicates that those compounds influencing the acute toxicity of histamine, indole or guanidine are the same compounds which the body normally uses in the processes of detoxication, cystine or one of the other sulfur-containing amino acids (cysteine or methionine), glucuronic acid, glycine, and ascorbic acid being the more commonly known detoxifying agents. To this list choline must be added.

TABLE II

Protocol of a Histamine Detoxication Series

(Values expressed in grams)

Compound	Preparation				
	No. 1	No. 2	No. 3	No. 4	No. 5
Histamine	2.8	—	—	—	—
Tragacanth Gum	—	0.25	0.25	0.25	0.25
Cystine	—	1.0	—	—	—
Glycine	—	1.0	1.0	—	—
Ascorbic Acid	—	1.0	—	1.0	—
Calcium Glucuronate	—	1.0	—	—	1.0
Volume	140.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.

0.6 gram/Kilo = L.D. 50 Subcutaneous

Solution No. 1 contains 20.0 mg. of histamine per c.c.

Detoxifying chemical or chemicals given orally 2 to 3 hours before histamine is given

Set	Number of Mice	Weight of Mice	Oral Dose Detoxifying Preparation	Preparation Number	Subcutaneous Histamine Dose	Number Dead	Per Cent Dead
1	50	18 gm.	—	—	0.54 c.c.	30	60
2	50	18 gm.	0.7 c.c.	2	0.54 c.c.	9	18
3	50	18 gm.	0.7 c.c.	3	0.54 c.c.	26	52
4	50	18 gm.	0.7 c.c.	4	0 54 c.c.	20	40
5	50	18 gm.	0.7 c.c.	5	0.54 c.c.	23	46

Choline has not been generally regarded as a detoxifying agent, but its action as a source of labile methyl would make it so.

Tables 2, 3, and 4 present protocols of single unit experiments with each of the toxic substances: histamine, indole and guanidine.

These tables are presented to clarify the methods of experimentation which are difficult to describe without the aid of such protocols. In each of these sets the maintenance ration was given for three days before the mice were used. It was felt that, inasmuch as indole and guanidine were produced in the intestine, oral tests were indicated. Histamine on the other hand is produced both in the intestine and in the tissues, hence subcutaneous tests were used.

Table 2 demonstrates a reduction in the percentage of deaths following

acutely toxic doses of histamine ranging from 8 per cent to 50 per cent. In this instance the toxic material was given subcutaneously, and the detoxifying chemicals were given orally. Table 3 demonstrates a reduction in the percentage of deaths following acutely toxic doses of guanidine acetate ranging from 8 per cent to 52 per cent. Finally, table 4 demonstrates a reduction in deaths due to acutely toxic doses of indole ranging from 0 to 24 per cent.

In an attempt to explain this marked effect in acute toxicity studies, the detoxified form of indole, indican, was determined in the urine of dogs following one gram doses of indole with and without the simultaneous ad-

TABLE III

Protocol of a Guanidine Detoxication

(Values expressed in grams)

Compound	Preparation						
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7
Guanidine Acetate	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Gum Tragacanth	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Glycine	——	0.5	——	——	——	——	0.5
Cystine	——	——	0.5	——	——	——	0.5
Calcium Glucuronate	——	——	——	0.5	——	——	0.5
Ascorbic Acid	——	——	——	——	0.5	——	0.5
Nicotinic Acid	——	——	——	——	——	0.5	0.5
Volume	25.0 c.c.	25.0 c.c.	25.0 c.c.	25.0 c.c.	25.0 c.c.	25.0 c.c.	25.0 c.c.

0.6 gram of Guanidine Acetate per Kilo = L.D. 50 oral
50.0 mg. of Guanidine Acetate per each 1 c.c.

Set	Number of Mice	Weight of Mice	Weight Dose Guanidine	Volume Dose of Preparation	Solution	Number Dead	Per Cent Dead
1	50	18 gm.	10.8 mg.	0.21 c.c.	No. 1	30	60
2	50	18 gm.	10.8 gm.	0.21 c.c.	No. 2	26	52
3	50	18 gm.	10.8 gm.	0.21 c.c.	No. 3	20	40
4	50	18 gm.	10.8 gm.	0.21 c.c.	No. 4	26	52
5	50	18 gm.	10.8 gm.	0.21 c.c.	No. 5	26	52
6	50	18 gm.	10.8 gm.	0.21 c.c.	No. 6	8	16
7	50	18 gm.	10.8 gm.	0.21 c.c.	No. 7	4	8

ministration of a mixture of detoxifying chemicals consisting of glycine, cystine, calcium glucuronate and ascorbic acid. The method used was that of Askenstedt.[17] This method is more an estimation than a determination but results check on several samples and from dog to dog. In one set of three dogs receiving indole alone, the indican value in terms of indigo was 79.75 mg. The first experimental set receiving the detoxicant showed a value equal to 28.70 mg. of indigo and the second set of three determinations on experimental dogs receiving indole and the detoxifying chemicals showed a value of 35.00 mg. of indigo. These values indicate mg. of indigo from 10 c.c. of urine. An observation in these dogs, the significance of which is not yet clear, was the black color of the urine following administration of

TABLE IV

Protocol of an Indole Detoxication Series

(Values expressed in grams)

Compound	Preparation						
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7
Indole	3.75	——	——	——	——	——	——
Gum Tragacanth	0.37	0.25	0.25	0.25	0.25	0.25	0.25
Cystine	——	1.0	1.0	——	——	——	——
Glycine	——	1.0	——	1.0	——	——	——
Calcium Glucuronate	——	1.0	——	——	1.0	——	——
Ascorbic Acid	——	1.0	——	——	——	1.0	——
Choline	——	——	——	——	——	——	1.0
Volume	75.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.	50.0 c.c.

0.5 gram of Indole per Kilo = L.D. 50 Oral

50.0 mg. of Indole = 1 c.c. of Preparation No. 1

Dose of detoxifying substance given orally 3 to 4 hours before indole was administered

Set	Number of Mice	Weight of Mice	Volume Dose Detoxifying Chemical	Preparation Number	Weight Dose Indole	Volume Dose Indole	Number Dead	Per Cent Dead
1	25	18 gm.	——	——	9 mg.	0.18 c.c.	17	68
2	25	18 gm.	0.5 c.c.	2	9 mg.	0.18 c.c.	9	36
3	25	18 gm.	0.5 c.c.	3	9 mg.	0.18 c.c.	10	40
4	25	18 gm.	0.5 c.c.	4	9 mg.	0.18 c.c.	17	68
5	25	18 gm.	0.5 c.c.	5	9 mg.	0.18 c.c.	8	32
6	25	18 gm.	0.5 c.c.	6	9 mg.	0.18 c.c.	18	72
7	25	18 gm.	0.5 c.c.	7	9 mg.	0.18 c.c.	9	36

indole unless the detoxifying chemicals were given simultaneously, in which event the color of the urine was normal. This black urine is seen following the ingestion of certain hydrocarbons, naphthalene, and most phenolic type compounds. In the case of phenol the coloration is due to the formation of hydroquinone or pyrocatechin or, generally speaking, the dihydroxybenzenes.

DISCUSSION

The action of detoxifying chemicals is not specific for the endogenously produced poisons under consideration in this paper but rather is a manifestation of a reinforcement of the processes used by the body in its defense against toxic chemicals, regardless of their nature. This type of therapeutic or prophylactic detoxication is equally effective against the products of the metabolism of the organisms which infect the body and the specific chemotherapeutic agents used in the treatment of disease,[18] as well as against a variety of poisons, to be reported separately. The problem of detoxication of absorbed toxic chemicals is the same as the problem of the detoxication of toxic chemicals produced within the body by an invading parasite. The general process of detoxication follows three lines: oxidation, reduction and

conjugation. Frequently, oxidation and reduction precede conjugation. The processes of oxidation and reduction of toxic chemicals are being subjected to intensive study, but it remains difficult to apply any practical methods of influencing these processes. Vitamin therapy doubtless owes a great deal of its effectiveness to the reëstablishment of an enzyme moiety and normal processes of oxidation and reduction which are concerned in detoxication. Thus, there is available at present but one process which can be used to facilitate detoxication: namely, the process of conjugation. In passive immunity the body's defense is reinforced by supplying it with additional preformed antibodies. In conjugative detoxication it is possible to supply the body with increased raw materials used in the processes of detoxication. The mechanism of conjugative detoxication is one of enzymatic action, and in the study of enzyme action it has been found that the concentration of the substrate is a vital factor in the speed of the reaction. Starting with zero concentration of the substrate, the velocity of the reaction increases with increasing concentration of the substrate, then remains constant for a considerable variation in concentration and finally decreases in very concentrated solution of the substrate. Obviously, the concentration of the substrate in the enzymatic processes of conjugative detoxication can be altered, and this is the single factor influencing the speed of the reaction that can be altered. This immediately suggests a type of prophylaxis and therapy which is used in this paper against the acute toxication of certain chemicals.

There are several questions to be answered before the logic of this therapy can be judged. First, are the compounds involved in detoxication sufficiently well known so that an attempt could be made to reinforce them? Second, is there actually a quantitative deficiency of these compounds, or can the body supply them in unlimited amounts? Third, will an increase in the circulating amounts of these compounds actually facilitate and speed up the rate at which conjugation and detoxication occur?

Certain of the compounds involved in conjugative detoxication are well known, and no attempt will be made to review this material as various excellent reviews on the subject are available.[19, 20, 21, 22, 23, 24] There is a certain specificity exhibited in the processes of detoxication. The compounds involved are glycine, cystine, glucuronic acid, glutamine, sulfates, acetates and ornithine. Ornithine is used only by the fowl in detoxication. Glutamine is a curiosity among detoxicating compounds, but the other above mentioned compounds are of importance in detoxication and, therefore, in vital economy.

Glycine is utilized in the detoxication of hundreds of toxic compounds. Generally, it can be stated that glycine combines with the carboxy group of organic acids. The rôle assumed by glycine can be taken over by glucuronic acid in many cases. This overlapping of specific detoxication channels is of vital significance in a rational application of detoxication in therapy and in prophylaxis. Glycine is not an essential amino acid and is not stored in

the body. It is furnished as required for detoxication reactions in much greater quantities than is supplied by the food. Griffith and Lewis [25] conclude that the rate of hippuric acid formation is directly proportional to the amount of glycine available. Hippuric acid is the conjugated product of benzoic acid and glycine. Experiments with both growing [26, 27, 28] and adult animals [29] have shown that the rate at which the organism can produce glycine for detoxicating purposes is distinctly limited, and in a fasting man it is this factor which eventually limits the output of hippuric acid when increasing doses of sodium benzoate are ingested.[30] Griffith and Lewis [25] found that the administration of glycine or protein digests rich in glycine [31] to rabbits receiving sodium benzoate increased the rate of excretion of hippuric acid. A number of other amino acids and other substances failed to produce this effect. These investigators suggest that the greater rate of synthesis of this compound results from the presence of increased amounts of preformed glycine in the organism. Briefly, therefore, one can state that although glycine may be synthesized in response to need for it in the detoxication reaction, an increased ratio of synthesis and excretion of a toxic substance is observed when an abundant supply of exogenous glycine is furnished. Glycine has a relatively slight effect in the detoxication of the endogenous type of toxic chemicals considered here. Its effect is marked in the detoxication of the sulfonamido type of chemotherapeutic agent.[18] A consideration of the type of compound rendered non-toxic by conjugation with glycine would lead to the conclusion that where conjugation is concerned, glycine would not detoxify histamine, guanidine or indole. The slight action exerted by glycine in this study is probably due to action by way of an enzymatic system.

Cysteine is a second amino acid used by the body in detoxication. Generally, cystine or methionine is the qualitative but not the quantitative equivalent of cysteine. Bromobenzene and other halogenated derivatives of benzene are the best known examples of compounds detoxified by combination with cysteine. Cysteine hooks into the benzene ring at the para position. Subsequently, the amino group of the cysteine is acetylated and the compound is then excreted. The body cannot synthesize the sulfur-containing amino acids, and, therefore, they are necessary components of the diet. Abderhalden's experiments on fasting dogs showed that the small amount of endogenous cystine is immediately used for such body needs as the formation of glutathione, taurine, and insulin.[32] More recently, White and Lewis [33] have studied the metabolism of bromobenzene in dogs on a cystine deficient protein diet and cystine rich protein diet, and they found that mercapturic acid formation parallels the cystine content of the protein. Stekol [34] has presented evidence indicating that the organism can supply cystine to detoxicate bromobenzene at the expense of its own tissues if no exogenous cystine or methionine is available. It is obvious that a distinct limit exists beyond which contributions of cystine for purposes of detoxication from the tissue of the body will result in a complete upset of body economy. White

and Jackson [35] have utilized bromobenzene in growth experiments in which they found that when this substance was incorporated in an otherwise adequate diet, the growth of white rats was retarded. The addition of either cystine or methionine readily overcame this retarding influence. This leads to the obvious conclusion that if the body is forced to deprive itself of its tissue cystine for purposes of detoxication, other vital functions involving cystine, such as growth, must suffer. Taurine and sodium sulfate failed to stimulate growth in animals fed bromobenzene. It seems that the sulfur-containing amino acids were specific in this respect. It is clear from the above that the detoxication of bromobenzene and other toxic chemicals takes precedence over growth requirements. The mode of action of sulfur-containing amino acids is doubtless through a sulfhydryl group. Cysteine, cystine or methionine are effective in the detoxication of any one of the three compounds herein considered (guanidine, indole and histamine). Here again, the potentialities of conjugative detoxication are remote. The sulfur-containing amino acids are regarded as the source of the sulfuric radical involved in the detoxication of indole by the formation of indican. In this instance we have demonstrated that the detoxifying chemicals actually inhibit the formation of indican rather than promote it. It is, however, highly probable that the detoxication may proceed by conjugation resulting in an as yet undetermined product. Our results show that methionine possesses a somewhat greater power as a detoxifying agent than does cystine or cysteine. The labile methyl supplied by the methionine may be responsible for this increment in detoxifying power. Both choline and methionine seem to function as sources of labile methyl, and choline and methionine both act in the detoxication of indole; hence, the conclusion that labile methyl explains the greater efficiency of methionine as compared to the other sulfur-containing amino acids. It can be stated that the sulfur-containing amino acids are effective in decreasing the acute toxicity of guanidine, histamine and indole. Again, whether this effect is due to conjugation, restoration of enzymatic activity, etc., it is not possible to state at the present time.

Glucuronic acid is the conjugating agent in an almost unlimited number of instances. The compounds usually have hydroxy groups or are aldehydes or ketones which through reduction are converted into primary or secondary alcohols. Glucuronic acid is quite capable of combining with organic acids, such as benzoic, etc. The glucuronic acid conjugates are particularly interesting since one is an ester type and the other is a glucoside linkage. All recent studies tend to show that glucuronic acid plays a much greater rôle in detoxication than was formerly thought. Quick [36] first isolated pure glucuronic acid compounds from the urine. Hemingway, Pryde and Williams [37] proved that conjugation with glucuronic acid occurred in the liver. In the present study, dihydroxyacetone, pyruvic acid and lactic acid were checked for detoxifying power because of the studies of Lipschitz and Bueding.[38] These workers demonstrated that surviving liver slices of

rabbits, rats or guinea pigs produced conjugated glucuronic acids from d-borneol, l-menthol, avertin or phenol. The production in the liver slices was increased by insulin and depressed by adrenalin. Glucuronic acid is, therefore, not a product generated by oxidation of carbohydrates, glucosides or maltosides, nor is free glucuronic acid conjugated freely with alcohols. The formation of conjugated glucuronic acids is, according to these investigators, a synthetic process from shorter carbon chains. Two further points are emphasized by these workers, namely: that heavy metal catalizes the formation of the glucuronates, and that phosphorylation is essential to the entire process. Dihydroxyacetone, lactic acid and pyruvic acid have no effect in the detoxication of the three compounds herein considered. Glucuronic acid on the other hand is effective against histamine, indole and guanidine. With the exception of indole, the toxicity of the other two compounds is probably counteracted by glucuronic acid through enzymatic systems rather than through conjugation. In the case of indole, it is suggested that the demonstrated decreased formation of indican would indicate conjugation along other lines, namely, to a glucuronic acid product.

Evidence of the importance of vitamin C in detoxication processes is extensive. It is well known that tissue concentration of vitamin C is markedly lowered by some of the bacterial toxins and other toxic materials, and that there is a reduced tolerance for such substances by animals whose vitamin C reserves are depleted. Ascorbic acid has frequently been indirectly connected with resistance to, or the detoxication of, histamine. Epstein [39] noted that large doses of vitamin C aided in the desensitization of patients suffering with bronchial asthma. Lemke [40] reported that vitamin C, when injected intravenously, into hypersensitive guinea pigs, desensitizes them. Hochwald [41] confirmed the observations of Lemke. Further extension of this effect of vitamin C in decreasing or abolishing the anaphylactic reaction was carried out by Hasimoto et al.[42] More recently, Yokoyama [43] reported that anaphylactic shock was prevented in sensitized guinea pigs by the injection of ascorbic acid immediately before the second injection of horse serum. If the horse serum was mixed with the ascorbic acid before injection, shock was also prevented, probably owing to the denaturation of the antigen. The Schultz Dale reaction of isolated intestine from sensitized guinea pigs was inhibited by vitamin C if it was added to the Locke solution five minutes before the horse serum. In similar conditions a slight reaction was obtained with isolated uterus, but it is considered that uterine muscle is more sensitive than intestinal. Raffel and Madison,[44] on the other hand, report complete inhibition of hypersensitive manifestations in only two of 16 guinea pigs treated daily with ascorbic acid. In this same vein, Ungar et al.[45] report that the treatment of tissues with ascorbic acid renders them less labile as regards the liberation of histamine. It seems safe to conclude that an inhibition of anaphylactic reactions does follow the administration of vitamin C and our observations, in which we have demonstrated a decrease in the acute toxicity of histamine through the

concomitant administration of ascorbic acid, would support this conclusion.

The preceding discussion clearly outlines the basis for the use of the detoxifying chemicals in prophylaxis and in therapy. Approximately 50 different compounds have been used in an attempt to determine those most effective. It is clear that the most effective compounds are those used by the body in the ordinary processes of detoxication. Cystine, glycine, ascorbic acid and calcium glucuronate are the most effective, and the mixture of these chemicals is generally more effective than any single one. Each of the effective chemicals is a physiological body constituent. They are obviously in themselves non-toxic. The exact mechanism of their action is not clear. Partially, it is undoubtedly one of conjugative detoxication, and it is perhaps a mass action effect. The enzymatic processes of detoxication are facilitated by increased concentrations of the substrate, in this instance the detoxifying chemicals. It is to be noted that the major portions of these detoxifying agents are physiological reducing agents. This fact leads us to assume that a restoration of the cellular moiety necessary for enzymatic action other than that of conjugative detoxication is in part responsible for the effects observed in this study. Fundamentally, this type of therapy or of prophylaxis consists in reinforcing the body's own natural processes of defense against toxic chemicals. It is aimed primarily at detoxifying the toxic substances introduced into the body or produced endogenously.

It is strange that despite the enormous literature on the processes of detoxication, only recently has any attempt been made to develop this field of therapy and prophylaxis. It is certain that one phase of any deleterious process is the detoxication of the chemicals injuring the body, and it is also true that any procedure whereby this detoxication is speeded up will decrease the concentration of the toxic chemical present at a given time in the body and aid materially in the alleviation of the deleterious process. The entire thought behind therapeutic and prophylactic detoxication is its use as an adjuvant to specific therapy. In certain types of disease, e.g., toxemia of pregnancy, in which the etiology is not known and no specific therapy has been accepted, it is suggested that results might be obtained using detoxifying chemicals.

This study is based upon the theory that the detoxication and elimination from the body of poisonous materials, of whatever nature, is accomplished by the use of chemical substances normally present in the body, the reserve supply of which is relatively limited. An attempt has been made to study the rôle played by certain of these individual substances in the process of detoxication; and also to apply this knowledge therapeutically in man and animals, in such a manner as to secure the greatest possible protection by means of their detoxifying activities.

Histamine, indole and guanidine represent groups of toxic chemicals produced endogenously. In acute toxicity experiments it has been found possible to decrease markedly the toxicity of these substances by the concomitant administration of certain physiological detoxifying agents: ascorbic

acid, glycine, glucuronic acid and cystine (sulfur-containing amino acid). Indican formation is inhibited by the use of these detoxifying agents.

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TULAREMIA; A REPORT OF FOUR CASES WITH UNUSUAL CONTACTS *

By Joseph H. Shaffer, M.D., F.A.C.P., *Detroit, Michigan*

When we consider tularemia, commonly known as rabbit fever, we are likely to dismiss it with the thought that it is a rather uncommon disease which is far removed from our every day medical experiences. In the past 28 years this disease, first recognized in California, has been found to cause illness in human beings in every state in the union. It is now known that tularemia in addition to affecting the rabbit, is a disease prevalent in 20 or more forms of wildlife in America. This paper calls attention to the occurrence of tularemia in individuals who have not handled rabbits or other game. Three of these patients were infected by domestic cats, and one became ill following the bite of a wood tick.

Case Reports

Case 1. An optometrist, H. G., a white male, aged 50, was admitted January 19, 1940, to the medical service of the Henry Ford Hospital. He complained of extreme exhaustion and ease of fatigue on slight exertion. Two weeks before admission he had headaches, muscle soreness and pains, shaking chills followed by fever to 102° F. He had drenching night sweats, and there was a slight, but irritating non-productive cough with tightness in the chest. The above symptoms had been attributed to influenza which was prevalent at that time. Three weeks before admission an itching pustular lesion appeared on the dorsum of the left hand. There were enlarged and tender epitrochlear and axillary lymph nodes in the left arm.

When examined the patient appeared weak and tired. The temperature was 99° F. The chief points of interest were the enlarged left epitrochlear and axillary nodes and the healing pustule on the dorsum of the left hand. The epitrochlear gland measured 9 cm. in diameter and was firm and only slightly tender. The lymph nodes in the left axilla were readily palpable and tender. The liver was 5 cm. below the costal margin in the right midclavicular line; the edge was firm and sharp, but not tender. The spleen was readily palpable but not tender. Chest roentgenograms were negative for areas of consolidation or enlarged hilar nodes. There was a crusted pustule with an umbilicated center on the dorsum of the left hand. This lesion was 1.5 cm. in diameter and was dark red; its appearance suggested a hair-follicle type of infection (figure 1).

There was a mild secondary anemia with slight jaundice. The leukocyte count was 5,350 with 70 per cent polymorphonuclear cells. The blood sedimentation rate was 28 mm. in one hour. The Kline exclusion test for syphilis was negative. The patient's blood serum agglutinated *B. tularense* 1:100. Agglutination for *B. abortus* was negative. When repeated February 2, 1940, five weeks after the onset of the illness, the patient's titer had risen to 1:320.

We were unable to elicit from our patient a history of exposure to rabbits or fowl. Further questioning later revealed that the family cat had limped for several weeks.

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Examination of the cat revealed a healing ulceration on the skin of the left hind leg, but the animal did not appear to be ill. It was the habit of the patient to fondle his pet as it reposed on his lap. The cat's blood serum agglutinated *B. tularense* 1:360. Agglutination with *B. abortus* was negative.

This patient was given sulfanilamide because of the low grade fever and adenopathy. He received a total of 165 grains over a period of three days when the drug was stopped because of nausea and vomiting. The blood sulfanilamide level had reached 5.9 mg. per 100 c.c. blood, but there was no improvement in the patient's condition during that short period of treatment.

The patient's left epitrochlear lymph node remained large and became progressively more tender and fluctuant. There was also increased redness and heat. In the fifth week the abscess pointed by rupturing through the capsule of the lymph node (figure 2). Simple incision was followed by drainage of several ounces of thick yellow-white

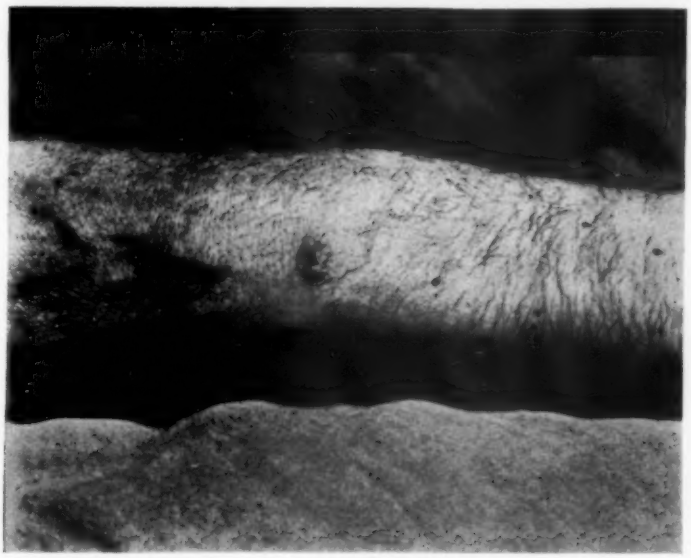

FIG. 1. (Case 1.) Tularemia infection in man contracted from house-cat. Hair follicle infection on dorsum of left hand two weeks after onset of illness.

purulent material. Culture on glucose-cystine-blood agar plate was negative. The incision continued to drain for three weeks, and the patient was not returned to his former state of health until eight months after his initial infection.

Case 2. E. D., a white male physician, aged 26, was bitten by a wood-tick while vacationing in Wyoming, in July 1940. There was marked localized itching, and within a few days an ulcer appeared at the site of the bite. The lesion was several mm. deep and the base of the ulcer was studded with elevated, yellow, pin-head sized nodules. The edges of the ulcer were elevated, smooth and rolled (figure 3).

The patient had experienced three weeks of fever, malaise and anorexia with a resultant weight loss of 14 pounds. The right axillary lymph nodes were enlarged and tender, and there was a nodular lymphangitis in the forearm. The leukocyte count was 12,800 with 70 per cent polymorphonuclear cells. The patient's blood serum agglutinated *B. tularense* 1:40 during the second week of his illness, and 1:160 by the third week. Culture from the ulceration on the forearm was implanted on

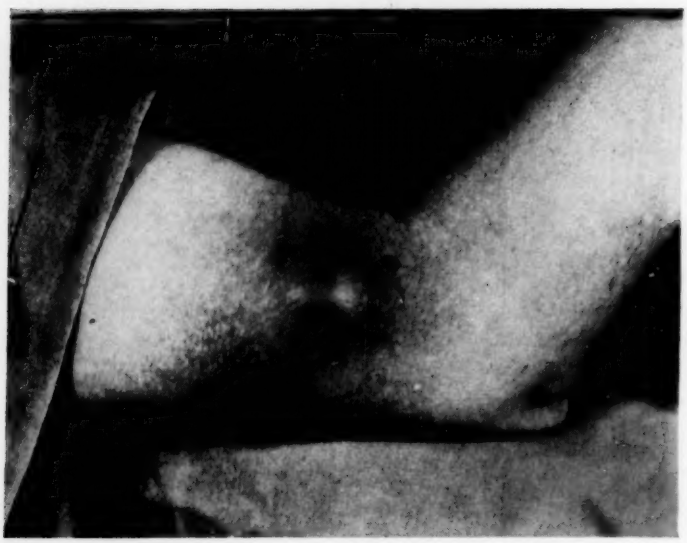

FIG. 2. (Case 1.) Abscessed epitrochlear gland five weeks after onset of illness. Simple incision and drainage now indicated.

FIG. 3. (Case 2.) Ulceroglandular tularemia. Print from kodachrome picture of skin lesion three weeks following an insect bite. The lesion remained an open ulcer for five weeks.

cystine-blood-agar; a small gram negative cocco-bacillus was isolated and was indistinguishable morphologically and serologically from *B. tularense*.* [1]

This patient was seen again in the eleventh week of his illness. He had regained 12 pounds weight, but continued to tire easily with physical exertion. His

* Tests done at the Minnesota Department of Health Laboratories.

blood agglutination titer had risen to 1:20,000 with Mulford antigen and 1:1,600 with (H. F. H.) antigen prepared in the hospital laboratory. The ulcer, which had drained for five weeks, was then covered with healthy pink scar tissue. The axillary lymph nodes were barely palpable. His strength had returned and he was able to return to full-time work. A progress blood test January 11, 1941, six months after the onset of illness, disclosed a blood serum agglutination of 1:5,000 with Mulford antigen and 1:2,000 with Michigan Department of Health antigen. He continues now in his usual good health.

Case 3. R. B., a 2-year-old white boy, received a bite on the left cheek from a domestic cat while visiting on his grandparents' farm not far from Detroit, on October 15, 1940. The boy became ill with nausea, vomiting and fever several days after

FIG. 4. (Case 3.) Infection of the face following the bite of a cat. Abscess continues to drain after three months.

he was bitten. The lymph nodes in the left cervical region became tender and swollen. There was anorexia followed by weight loss, and the boy's color and health in general were poor for several weeks. The wound was cleansed by the mother. When a physician was first consulted about December 15, 1940, a deep abscess of the left face was lanced and purulent material escaped. No culture was taken.

This patient was brought to the Surgical Clinic of the Henry Ford Hospital, January 21, 1941 because of the failure of the lesion on the face to heal. This was three months after the onset of the illness. The boy was not acutely ill. There was an indurated, swollen area just below the left malar prominence. The tooth marks

made by the cat were visible, and at the lower site where the teeth had punctured the skin there was a brown crust of dried serum (figure 4). Moderate pressure caused straw-colored serum to exude from beneath the crust. The serum was sterile when cultured on cystine-blood-agar. The left cervical lymph nodes were enlarged, firm and tender.

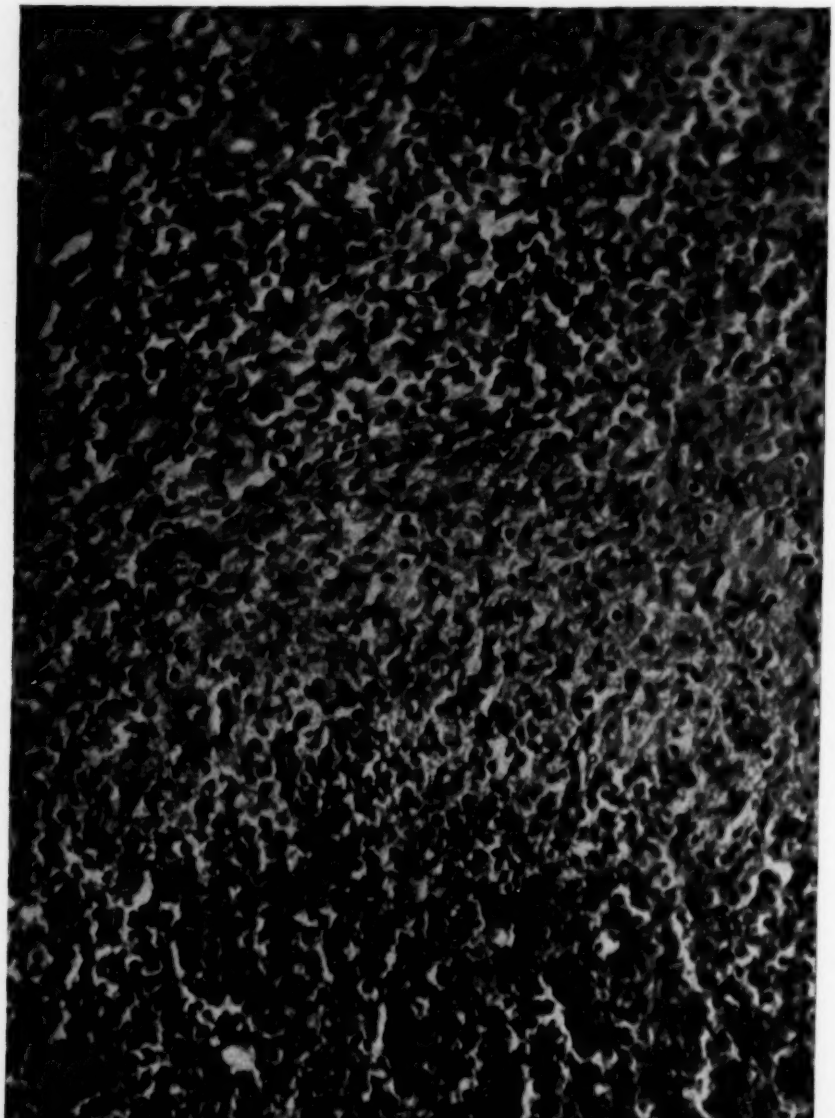

FIG. 5. (Case 4.) Tularemia. Section of lymph node removed at biopsy. (Courtesy of Dr. Frank W. Hartman.)

This boy's blood count was normal, but his blood serum agglutinated *B. tularense* 1:200 with Mulford antigen and 1:50 with Michigan State Board of Health antigen.

The cat that bit the boy was brought to the hospital January 28, 1941. It was a huge animal and it did not seem to be ill. There were no skin lesions. The cat's blood agglutinated *B. tularense* 1:50 with Mulford antigen and 1:25 with Michigan State Board of Health antigen. Postmortem examination of the cat revealed no gross or microscopic lesions of tularemia.

Case 4. C. F., a white female student, aged 15, had noticed a tender swelling in the left axilla which had appeared insidiously some four to six weeks before. There were no other complaints. Although she was unaware of it, her temperature was elevated to 99.4 degrees F. There was a single tender and enlarged lymph node,

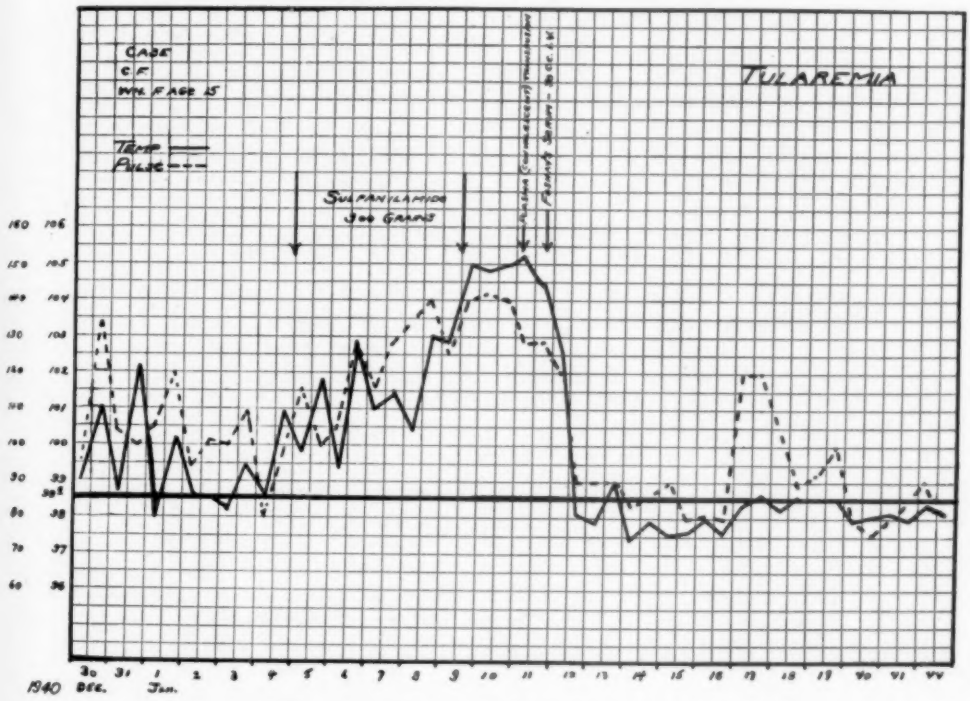

FIG. 6. (Case 4.) Successful treatment with plasma transfusion from recently recovered tularemia patient, and Foshay's antitularemia serum.

approximately 3 cm. in diameter, in the anterior portion of the left axilla. There were no other noteworthy features.

The erythrocyte count was 4,860,000 with 13.1 grams (84 per cent) hemoglobin. The leukocyte count was 7,000 with 64 per cent polymorphonuclear cells. Chest roentgenograms revealed some increase in the hilar shadows.

On December 30, 1940, four days after the above examinations, the enlarged lymph node was removed for biopsy. The specimen consisted of two small well-encapsulated lymph nodes, the larger measuring 3 by 1.5 by 1.5 cm. The capsule was thickened and infiltrated with round cells. Scattered throughout the gland were several areas of necrosis which were not caseous in character but contained polymorphonuclear cells. Surrounding the necrotic areas which were oval in shape, were many round cells and some epithelioid cells arranged more or less concentrically. The pathologist's

impression was that the specimen was "lymph-node, chronic granuloma, probably tularemia" (figure 5).

With the above report in mind the patient's history was rechecked. It was learned that the family cat had been irritable and mean and had scratched and bitten members of the patient's family. The patient remembered a slight abrasion on the left index finger where the cat had bitten her some weeks before. Very little concern was caused by the bite inasmuch as it healed without difficulty.

The patient's blood serum agglutinated *B. tularense* 1:50 with Mulford antigen. There was a foul discharge from the incision in the left axilla. The leukocyte count had risen to 15,950 with 85 per cent polymorphonuclear cells by January 9, 1941. The temperature rose to 105° F. Sulfanilamide had been started on January 4, 1941 and was discontinued on January 9 after approximately 300 grains had been administered without beneficial result. The agglutination titer had risen to 1:100 with Mulford antigen. The temperature reached a peak of 105.2° F. by January 11, 1941; the pulse rate was 140 per minute and the leukocyte count had risen to 16,000.

The patient was given immune serum in the form of a plasma transfusion of 200 c.c. from a recently recovered tularemia patient whose blood serum agglutinated *B. tularense* 1:5,000 with Mulford antigen. The blood plasma was given at 11:30 a.m. and in the afternoon she was given 30 c.c. of antitularemic goat serum that had just arrived from Dr. Lee Foshay. The goat serum was given in one dose intravenously without immediate reaction. The patient showed striking symptomatic improvement within a few hours. The temperature dropped to 102.6° F. by the next morning. January 12, 1941. By afternoon the temperature and pulse rate had returned to normal and there was no further fever (figure 6). On the fifth day after serum therapy the patient had an urticarial reaction, but she continued to improve generally and left the hospital on the twentieth day. Her blood serum at the time of discharge agglutinated *B. tularense* 1:1,000 with Mulford antigen.

Two other children from the same family had had contact with the cat. One child had a weak agglutination titer for *B. tularense;* the other had a negative blood test, although the right epitrochlear lymph nodes were slightly enlarged. Both children remained well.

The family pet cat was brought in for examination. Its blood serum did not agglutinate *B. tularense.* Gross and microscopic examination of the tissues was negative for tularemia. It was thought that the patient and her younger brother and sister were infected from the contaminated animal which remained free of infection. The family resided in a suburban community where the cat could hunt in nearby fields.

Tularemia in Man Traced to Infected House-Cats. In addition to the cases presented in this paper, a review of the literature discloses that Collins,[2] in 1933, reported ulceroglandular tularemia in a man 14 days following a bite on the index finger by a six month old kitten. The patient's blood serum agglutinated *B. tularense* 1:1,280, while the cat's blood serum agglutinated the organism 1:80.

Rudesill,[3] in 1937, reported tularemia in a woman following the bite of a cat or one of its two nursling kittens. The mother cat had fed on a dead tularemic rabbit. On the thirteenth day the patient's blood serum agglutinated *B. tularense* 1:80, and on the seventeenth day it was 1:640. The woman recovered after an illness of two months. The mother cat recovered but the two kittens died.

The Public Health Bulletin of April, 1940, reported a total of 13 persons

with tularemia after contact with cats, two having been scratched and 11 having been bitten.[4]

Susceptibility of the Domestic Cat to Infection. McCoy and Chapin,[5] as early as 1911, noted that the domestic cat was susceptible to tularemia. Cats were noticed with buboes from natural infection. They inoculated five cats with a strong emulsion of a 48 hour agar culture; one cat died on the eighth day and four cats developed buboes and ulcerations. The following year the same workers inoculated four cats subcutaneously with large doses of an emulsion from the liver of a guinea pig dead of tularemia. The cats remained well, whereas control guinea pigs died.

Simpson,[6] in 1929, reviewed experimental work of Wherry, Green, Wade, and Hanson, and Francis pertaining to the susceptibility of the domestic cat to infection with *B. tularense*. Francis,[7] in 1924, infected two cats, one by repeated feedings with infected lymph nodes from tularemic guinea pigs, and another by subcutaneous inoculation with a virulent culture of *B. tularense*. Both cats subsequently died of tularemia. It therefore seems that the domestic cat's susceptibility to *B. tularense* has, on the basis of experimental work reported to date, been established. The cat has been listed among the mildly susceptible animals.

Reservoir of Infection in the United States. Literature on tularemia includes reports of the prevalence of the disease in all sections of the United States. Since 1925 tularemia has been recognized in 10 foreign countries. Investigators have reported tularemia in more than 24 forms of American wildlife such as wild rabbit, coyote, beaver, skunk, raccoon, fox, rat, squirrel, woodchuck, sheep, meadow-mouse, horned owl, pheasant, fish, muskrat, hog, lamb, dog, wood-tick, horse-fly, and other insects.

Water-borne infection, presumably from contamination with animals, dead or alive, has been recognized. Positive cultures were obtained on samples of water taken from Montana streams, and tested by the Rocky Mountain Laboratory of the Public Health Service at Hamilton, Montana.[8]

House pets, such as the domestic cat, when kept in rural communities such as was the case in the three instances reported in this paper, may hunt in the fields and thereby become contaminated or infected with *B. tularense*. Such a possible source for illness in man should not be overlooked.

Summary

1. Four cases of ulceroglandular tularemia in man, occurring without contact with rabbits, have been reported. Three of the patients became ill after contact with pet house cats, and one became ill following the bite of a wood-tick.

2. The susceptibility of the house-cat to infection with *B. tularense* has been demonstrated experimentally by others. Tularemia in man may follow the bite or scratch of a pet cat; such a source of infection in man should

not be overlooked, especially in suburban and rural communities where the cat may hunt rodents of the field.

3. Attention is called to the widespread prevalence of tularemia, not only in rabbits, but in many forms of American wildlife.

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FACTORS WHICH MAY INFLUENCE SENESCENCE*

By Nathan Smith Davis III, M.D., F.A.C.P., *Chicago, Illinois*

In any discussion of the factors which may influence senescence, consideration must be given to clinical observations and research and to animal experimentation. Unfortunately there has been relatively little investigation of the problems of involution. Indeed, until recently the subject has attracted little attention. Funds for any such prolonged studies have always been difficult to obtain. As the factors that influence senescence in the experimental animal may not have the same effect on the involuntary processes of man, it will be necessary to use both animal experimentation and clinical research in such studies.

Carcinoma, diabetes mellitus, the arthritides of advancing years, arterial hypertension, atherosclerosis and other "degenerative diseases," and such changes as premature graying of the hair and baldness, are generally believed to be influenced by heredity. It apparently determines not only the particular "degenerative disease" developed by the members of one or more generations of certain families, but also the age at which the disease first makes its appearance. It is, however, often difficult to differentiate between the true hereditary factors, those carried by the genes, and those included under the term "constitution."

"Constitution" is, in part, determined by heredity, and in part by environment. Social, economic and educational factors, familial habits of eating and living, occupation, the climate, the composition of the soil and water and of the food where an individual is born, where he grows up and where he spends his mature years, all have their effects.[1] The structure of the teeth of the people who have always lived in Deaf Smith County, Texas, and their resistance to caries, illustrate the influence that soil and water conditions may have on "constitution."[2] Heredity and environment may both contribute factors which so modify cellular chemistry that they determine the type of involuntary change and the age at which it first appears.

Warkany and Nelson have reported that congenital malformations develop in about one-third of the offspring of female rats bred while on Steenbock and Black's rachitogenic diet No. 2956.[3] They also found that the same female would produce offspring all of which were normal, if 2 per cent of dried pig liver were added to the diet. It requires a frankly deficient diet to produce such gross abnormalities. The nutritional status of the sire at the time of conception was found to have some effect on the offspring, but that of the female was of much greater importance.

It has been conclusively proved that poor and undernourished women are more apt to have spontaneous abortions at almost any stage of pregnancy,

* Read at the St. Paul meeting of the American College of Physicians, April 23, 1942.

and to have more stillbirths and offspring who die during the first year of life, than do those who are better nourished.[4] It is also known that the mother who has a chronic or severe acute illness during her pregnancy is apt to have an experience similar to that of malnourished mothers. In either case the children are not so strong as those born to healthy well-nourished women. Too frequent pregnancies may so weaken the mother that the results are the same.[5] It seems, therefore, that the "constitution" of a human being is influenced by the genes inherited from its parents, by their nutritional status and health at the time of conception, by the nutritional status and health of the mother throughout pregnancy and until supplemental feedings are started, and by environmental factors.

The health, nutrition and environment of the human being throughout life may modify the effects of heredity and "constitution" and the development of involutionary changes. According to Warthin, the loss of permanent teeth should not commence before the age of 60 is reached.[6] Yet malnutrition during infancy and childhood, plus the diseases that are more prevalent among the poor, who are ill-fed, ill-housed and ill-clad, have caused many young adults of the British Isles and the United States to lose many of their teeth.[7] To be sure, the loss of teeth due to senescence is of a different character from that due to caries, pyorrhea, alveolar abscess, etc. However, were it not for these pathological changes in the teeth and gums that are now believed to be caused by improper diet and systemic disease, the teeth would have remained to undergo the regular involutionary changes of aging.[8]

The relation of proper nutrition and absence of disease to normal growth and to normal cellular chemistry is well established. Reference need only be made to the work of Todd and his collaborators to illustrate the importance of these factors in the proper development of the skeleton and teeth.[9] Their effect on all other tissue cells must be as great. McCay has demonstrated in rats that the quality and quantity of the ration is of great importance in determining their longevity.[10] He found that a diet that was qualitatively adequate but quantitatively deficient (a diet that retarded growth) greatly prolonged the life of rats. It seems logical to suppose that proper nutrition, quantitatively as well as qualitatively, is of at least as much importance in prolonging maturity and postponing involution in the cells of human beings as it is in prolonging the life of the experimental animals.

For proper nutrition, a diet is required that contains the vitamins, minerals, amino acids and other elements that are essential to the normal utilization of the amounts of carbohydrates, fats and proteins it contains. The relative proportions of the fats, proteins and carbohydrates must also be correct, and the caloric value of the diet such that it satisfies the needs of the particular individual. The individual needs during maturity are not just what they were during the growth period or what they will be in old age.

The discovery of more effective methods for the prevention, diagnosis and treatment of many of the epidemic bacterial and virus diseases and for

the feeding of infants and children has already reduced the morbidity and mortality rates of infants, children and young adults. As a result, the life expectancy of these age groups has been materially increased.[10] There has, however, been but little prolongation of the life expectancy of those who have survived to the fourth and fifth and later decades. Indeed, it is popularly believed that the degenerative diseases are now appearing earlier in life than they formerly did, and that they are causing more deaths in young and mature adults. There is no indisputable evidence as to whether or not there has been a real increase in the number of people who develop involutionary changes prematurely.[12] It is certain that little has been learned about the onset, early diagnosis, prevention or treatment of these conditions.

Normal growth requires good health, proper nutrition and absence of disease. Those who have been chronically ill-fed, ill-housed and ill-clad suffer more from disease than do their well-fed, well-housed and well-clad contemporaries who are also apt to live longer lives. Historical evidence shows that this has been true of all races and of all age groups throughout the centuries.[18] Experimental work and clinical investigation have developed a fairly accurate knowledge of the nutritional requirements during the growth period. Almost no work has been undertaken to determine the diet that is optimal during maturity, or the one that is most effective in postponing the involutionary changes of senescence.

The work of Williams and his collaborators on the vitamin content of tissues indicates that the organs studied contain and probably require different amounts of the various vitamin B factors at different ages.[14] It seems likely that the content and requirements of the various tissue cells for the other vitamins, for various minerals and for the essential and non-essential amino acids also differ and vary with increasing age. They have also found that feeding hens on a diet enriched with pantothenic acid causes the other "B vitamins" to be altered in their distribution in the chicks hatched from the eggs. This indicates that the different vitamin B factors are not acting entirely independently.[15] Furthermore, it has been shown that a relative disproportion of some of these essential nutriments in the diet may be harmful. Certain of them are known to have a stimulating effect on one organ and an inhibitory effect on another.[16] Even the vitamins may not always be as harmless as we have been led to believe.

As more is being learned about cellular chemistry, it becomes more and more evident that the amounts of vitamins, minerals and essential amino acids required, depend on the relative and absolute quantities of carbohydrate, fat and protein in the diet. This is to be expected, for these essential elements participate in the formation of the enzymes and hormones required to catalyze the series of chemical reactions that take place in the tissue cells and result in the production of heat and energy. The problems of senescence will undoubtedly be solved when cellular chemistry can explain the involutionary changes that characterize it.

Initial moves toward such solutions for these problems have already been

made. DuVigneaud and his co-workers have found that biotin may have a carcinogenic effect.[17] Rhoads and others have shown that the vitamin B complex of yeast has an anti-carcinogenic effect in animals that have been fed "butter yellow."[18] What serves as the carcinogenic agent in the development of spontaneous cancer in experimental animals or in man, or in particular organs, has not yet been determined. It has been shown that the vitamins in the diet make a difference in cancers other than those induced by "butter yellow."[15] Adequate amounts of methionine and cystine and other unidentified protein factors are necessary for normal liver function.[19] Tyrosine or phenylalanine is necessary for normal thyroid, pituitary and adrenal function.[20] The effects of a deficiency of iron, calcium, phosphorus or iodine in the diet have received a great deal of attention, but little is known about the effects of a deficiency of some of the other minerals that are regularly present in human tissue in minute amounts.[21]

Numerous pathologic and clinical observations and a mass of experimental work support the theory propounded by Leary, that atherosclerosis is caused by a disordered cholesterol metabolism.[22] Winternitz believes that these lesions develop in the scars of subintimal hemorrhages.[23] Both may be right. The disordered cholesterol metabolism may cause the development of atherosclerosis in those individuals whose diet contains fat in amounts that are not in proportion to its carbohydrate, protein, vitamin, essential amino acid and mineral content, and therefore is not utilized as it should be by the cells of the body. The subintimal hemorrhages may develop because of some other type of relative or absolute dietary deficiency. In this connection, it must be remembered that in the presence of infection, a diet that has been adequate in all respects may become at least relatively deficient. Furthermore, different diets of equal caloric value may be adequate, relatively or absolutely deficient in their content of one or more of the essential elements.

There is much evidence that nutrition is of great importance in the treatment of some forms of bone and joint disease that are common in older people.[24] Proper nutrition has also been found of value in the treatment of heart failure and for the relief of psychoses in aged individuals.[25, 26] This does not mean that the "beriberi heart" or a niacin deficiency psychosis is present in all such cases.

The ischemic kidney of Goldblatt has a diminished supply of oxygen and of all other nutriments.[27] It has been shown that anoxemic renal tissue, in vitro, produces pressor amines, as it cannot normally metabolize amino acids.[28] Such tissue will in time form renin, a protein-like substance that has no pressor effect. It is theoretically possible that the series of chemical reactions in the renal cells could be arrested at the same point, and might form the same products when the oxygen content of the blood is normal but the required catalyst lacking. Braun-Menendez and his co-workers have shown that renin may be formed by the kidneys of normal dogs that are in shock because of excessive hemorrhage.[29] This group of Argentinian in-

vestigators and the group working with Page in Indianapolis [30] agree that the inert renin is formed in the ischemic kidney, enters the blood stream, where it reacts with "hypertensinogen" or "renin activator" to form "hypertensin" or "angiotonin." The two groups do not agree as to the exact rôle of these compounds; as to which are enzymes and which substrate. They agree that the kidney may produce a depressor substance which is called "hypertensinase" by the Argentinians. Infection in the kidney may cause hypertension. The products of bacterial growth may destroy or inactivate catalysts or prevent their formation, and produce the same changes in renal cellular chemistry that are caused by ischemia.[31] It appears, based on the findings in experimental animals, that the bacteria in the intestinal tract may synthesize or destroy vitamins in quantity according to the strains present and the character of the milieu in which they live.[32] A dietary deficiency that prevented the formation of these catalysts might well have the same effect.[33]

Infections such as cholecystitis, tonsillitis and others, both chronic and acute, are known to modify cellular chemistry by inactivating catalysts, by inhibiting their formation or by interfering with the secretion and action of hormones. The unfavorable influence of such infections on diabetes mellitus, coronary heart disease and arthritis, for example, is known to all internists.

Thyroid and other endocrine dyscrasias and the metabolic disturbances of advancing years may be caused by chronic foci of infection or by chronic minimal relative or absolute deficiencies of the vitamins, minerals, amino acids or other essential nutritional elements required for normal cellular activity.[34] Anoxia may also alter their metabolism. The dysfunctions of the endocrine glands result in an hyposecretion or hypersecretion of normal, or in the formation of abnormal hormones which will alter the chemical reactions in most, if not all of the tissue cells. They may thus initiate or accelerate the involutionary changes of senescence.[35]

Anoxia, infection and malnutrition may cause similar or even identical alterations in the series of chemical reactions that normally take place in the cells of all tissues and organs. Chronic mild infections, chronic minimal or relative dietary and oxygen deficiencies may have effects all out of proportion to their magnitude. They may instigate changes which become self-perpetuating and steadily increase the resulting functional and organic changes. For example, renin may begin to be formed because of a pyelonephritis. The hypertension formed when it reacts with hypertensinogen causes an ischemia of the kidney. This causes more renin and hypertensin to be formed. After such a vicious circuit has been in operation for some time, it may cause enough anatomic change to perpetuate it even after the primary cause is removed. Such a process will account for the insidious onset, prolonged course and gradually increasing severity of the degenerative diseases.

Many chemical compounds may react with the respiratory enzymes and

inhibit their catalytic action. As a result, some of the remedies used in the treatment of disease may, especially if used indiscriminately, produce serious complications. Cinchophen, amidopyrin, acetanilid, the barbiturates, the thiocyanates and the arsenicals probably are toxic because of some such action. It has been shown that the sulfa drugs are active therapeutically only because they replace a nutritional factor that is essential for the growth of the bacteria against which they are effective.[36] Unless this factor, similar in chemical composition to the sulfa drugs, is present in sufficient amounts, the cellular chemistry of the patient may be similarly affected. French and Weller report that an interstitial myocarditis with eosinophilic cellular infiltration was found in 126 out of 283 necropsies on patients who had received one of the sulfa remedies and in none out of 1423 who had not received any of them.[37] Incidentally, it has been shown that well-nourished individuals tolerate some of these remedies better than do those who are ill-fed. For example, an ascorbic acid deficiency decreases tolerance for the arsenicals.[38] Acute infections may also lessen tolerance for certain drugs.

Deplorable is the popularization of the indiscriminate use of alkalies to neutralize the "acidity" that exists only in the minds of advertisers, and to neutralize normally acid gastric juice. Such modification of peptic digestion can cause an adequate diet to become deficient. Excessive self-medication with alkalies may also cause alkalosis and renal damage.[39] Many of the dusts, gases and chemicals to which employees in industry and urbanites may be exposed, may also modify cellular chemistry. It has been suggested that the carbon monoxide and gasoline fumes inhaled by those riding in or driving motor cars may have some such effects. The ingestion for any length of time of compounds that alter biochemical processes should be expected to promote the involutionary processes that cause the degenerative diseases.

Many of the diets that have been prescribed or advertised for weight reduction are more injurious than the relatively high calorie diets that caused the obesity. Unfortunately, some of the diets of most value in the treatment of certain diseases are of necessity deficient in certain essentials. Patients may continue on these diets for much longer periods than their physician intended, and may develop "sub-clinical" or clinical deficiency states.

McCay's finding that a qualitatively adequate but quantitatively inadequate diet prolongs life in rats would indicate that a diet low in caloric value, which contained the required amounts of all the essential nutrients, should be of value in the prolonging of maturity and in the arresting or postponing of the involutionary changes.[10] His experimental work is confirmed by the finding that the life expectancy of men and women past the age of 40, who are underweight, is greater than that of those who are normal in weight. Both these groups will probably outlive all those who are overweight.[40]

The involutionary biochemical processes which lead to senescence may be influenced by all factors which in any way modify cellular metabolism. Much research and experimentation will be required to determine the exact

nature and relative importance of the factors which interfere with normal cellular chemistry so as to initiate the progressive involutionary changes that result in senescence. The factors that now seem to play an important rôle in the initiation and continuation of these metabolic changes, are: (1) Heredity; (2) The health and nutrition of the parents at the time of conception; (3) The health and nutrition of the mother during pregnancy and while nursing the baby; (4) The mild or severe, acute or chronic illnesses that the individual may have at any time during life; (5) Nutrition, its quantity and quality, and its relation to the needs of the particular individual at all periods of life; (6) The environment in which the individual grew up, worked and lived; his occupation, habits and mode of life; (7) The particular gases, dusts, chemical compounds and drugs ingested by accident, while at work or play, and on prescription.

These and other factors affect the rate of growth, the duration of maturity, and the onset and progress of senescent changes. But even under optimal conditions, involution will not be prevented, as it is a normal process in all living cells. Though its ultimate development is inevitable, the positive identification and the elimination, insofar as it is possible, of the factors that are responsible for the premature onset and abnormally rapid development of the involutionary changes of senescence are among the most important problems now before the medical profession.

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PERTINENT PROBLEMS OF GERIATRIC MEDICINE*

By Edward J. Stieglitz, M.S., M.D., F.A.C.P.,
Washington, D. C.

Geriatric medicine is that branch of medical science which treats of the elderly in all their physiologic and pathologic relations. Its problems are not confined to those patients actually senile, for the infirmities and disorders of later years arise insidiously far earlier than their clinical manifestations. Aging, as a process or series of processes, is continuous. It starts at conception and terminates only with death. Aging is a part of living. To arrest aging, therefore, would mean destroying life. Evolution, or growth, and involution, or atrophy, occur simultaneously throughout the life span. Even during fetal life localized atrophies occur, as in the involution of the branchial clefts. Growth of certain cells persists unto the end. These two antagonistic phenomena of aging, occurring asymmetrically at variable rates in different individuals and in different tissues, structures and systems of the same individual at different times, determine the rate and character of senescence. To age is to change.

Age is relative. Aging changes do not conform to rigid calibration on the scale of chronologic time. Biologic age and chronologic age are not necessarily the same. Though they may occasionally coincide, this is the exception rather than the rule. There are many of us physiologically older than our elapsed years and a few younger than our chronologic age. Furthermore, no one individual is of uniform physiologic age throughout. The rate of aging varies with certain cell types and with whole functional units or organs. For example, the cells of the epidermis are relatively short lived and are being replaced constantly, whereas the nerve cells of the cerebral cortex are not replaced as long as the organism survives. The female organs of reproduction go through a relatively rapid involution at about the time of the climacterium, but senescence of other structures is not accelerated at this time. Biologic age, therefore, is a composite sum of the extent of aging of all the constituent structures.

The basic concept that *aging brings change* is the foundation stone not only of young geriatrics, but of its older brother, pediatrics. These two special fields have much in common, not because of the platitudinous definition of senility as a second childhood, but because it is at the beginning and end of the life span that the consequences of aging are most conspicuous. Pediatrics made its greatest advance when it was realized that the child is not merely "the little man," but presented structural, functional, metabolic and immunologic characteristics *peculiar* to the periods of infancy and child-

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hood. Senescence, like growth and development, brings insidious and occult changes affecting all the structures and activities of the individual. The elderly are not just "old people"; they are physically and mentally *different* men and women than in the days of their young maturity. These changes are significant in the practice of medicine. Normality is not a fixed point but a series of variables which change with age. Recognition of these variables is essential in diagnosis. The early manifestations of incipient disease are readily confused with the changes of senescence. Disease, after all, rarely, if ever, introduces new phenomena; the manifestations arise from exaggerations or distortions of normal reactive mechanisms. The symptoms, signs, pathogenesis, course, prognosis and therapy of disease are all altered by the basic biologic changes of aging.

How old is old? There can be no unanimity as to just where geriatrics begins any more than there is complete agreement as to where pediatrics ends. It is necessary, however, to have some demarcation even if arbitrary. Limiting geriatrics to the care of the senile would completely ignore the significant fact that the changes of senescence begin many years earlier. Involutional changes, however, are not normally significant before the peak of maturity. It is, therefore, pragmatic to consider that the majority of clinical problems peculiar to geriatrics start at about 40 years of age, the approximate meridian of life. This does not imply that all of us over forty are decrepit and infirm by reason of senility, but from this age onward occurs the insidious accumulation of involutional phenomena whose later consequences constitute senility. The so-called degenerative disorders become conspicuously more frequent at this point in the life span. The menace of these chronic and progressive diseases is greatest from 40 to 60. If health can be maintained during these two critical decades, the likelihood of long disability and uselessness from chronic illness after 60 will be reduced immensely. Obviously, far more can be accomplished for the aging than for the aged. The aged represent the consequences of senescence; the character of involution determines the rate and extent of infirmity in senility. Therefore, geriatrics must include care and guidance during the period of senescence. An attitude of prophylaxis and preparation during maturity is essential if geriatrics is to prove truly effective.

Until recently the biologic problems of aging and geriatrics held largely academic and theoretical interest. This is no longer true. There is true urgency in the need to know more about aging and to apply more effectively that which is already known.[1] In the last 50 years preventive medicine, sanitation and vastly improved pediatrics have raised dramatically the age of our population. The major factor has been the saving of young lives by control of infective diseases. The increase in average age of the nation was accelerated in the last decade. War can but further exacerbate the situation.

Only a few figures suffice to reveal the present and impending importance of geriatrics in national health. In 1850 the average life expectancy at birth was 40 years. In 1900 this had risen to 47 years. Since the turn of the cen-

tury the rise has been quickened; in 1930 expectancy was about 60 years for white members of the American population, and in 1940 the average expectancy at birth was 63 years. An increased average expectancy at birth of 16 years (from 47 to 63) in but 40 years elapsed time constitutes such conspicuous handwriting on the wall that no apology for stressing the importance of geriatrics is needed.

In 1900 only 17 per cent of the total population of the United States were 45 years old or more. In 1940, 26.5 per cent exceeded 45 years of age. Conservative projection results in the estimate that in 1980 more than 40 per cent of the population will be over 45.[2] The median age of our population increased from 26.4 years in 1930 to 28.9 years in 1940, a rise of two and one-half years within a single decade. The numerical increase in the elderly is far greater than most of us realize. The total population of this country increased 7.2 per cent in the 10 years from 1930 to 1940, whereas those 65 years or older increased 35 per cent in the same interval. There are now approximately nine million persons of 65 or more in the United States.[2]

The implications of these facts are too vast to be considered here. The situation is without precedent. In the past, conspicuous shifts in population structure have arisen as results of destructive forces such as wars, famines and pestilence, but always the changes were in the direction of relative increase in youth. The less fit failed to survive. Today we are faced with the enhanced survival of less vigorous youths because of the protection of medical science and the lessened rigors of modern civilization. The apparent boon of increased longevity may become a curse. Longevity without health is more than individual or personal tragedy. In the aggregate it becomes a dangerous economic burden upon the nation. The social burden of chronic physical and mental illness among senescents is already immense.[3] It is steadily increasing.[4] We can ill afford additional loads now. Contrariwise, however, longevity with health, prolonged usefulness and productivity can be made into an incalculably valuable asset, for there exists in the elderly an immense, largely unutilized and little appreciated reservoir of accomplishment. Upon the balance sheet of our human resources chronic illness with long and progressive disability and the failure of society to employ many functionally capable among the elderly must be recorded as liabilities. Offsetting these are the potential assets of wisdom, judgment, accumulated skills and the desire to serve characteristic of later maturity. These are available, if health is maintained. The effectiveness of geriatric medicine, particularly in its preventive aspects, will determine the final balance. This heavy responsibility rests squarely upon the medical profession, though the majority of its members are unaware of it.

Many misinterpret the objectives of geriatrics as being limited to the prolongation of life and the relief of suffering. Such is a most inadequate concept. Geriatrics can and should aim far further than this. The normal life span of any species has definite biologically determined limits. There

is no desire to arrest aging. To do so would mean terminating life. Rejuvenation is a myth begotten of wishful thinking. Proper medical guidance, however, can prevent, retard or control disease so that disability may be postponed until true senility causes infirmity and thus add to the health, vigor and usefulness of the later years. The primary objective of geriatrics has been most brilliantly epitomized by Piersol and Bortz.[5] "The society which fosters research to save human life cannot escape responsibility for the life thus extended. It is for science not only to add years to life, but more important, to add life to the years."

How may this desirable objective be attained or approached? All manner of therapeutic measures are needed; it is impossible to answer in full at this time.[6] But if we classify therapeutics by its objectives rather than its methods, the issues are simplified. Well-known and conventional are therapy for prophylaxis, for cure, and to palliate symptoms. The effectiveness of prophylactic treatment, however, is conditioned by the precision and completeness of knowledge concerning the etiology of a disorder. Herein geriatrics is severely handicapped in contrast with pediatrics, for our understanding of the etiologic factors of most of the disorders of later years is nebulously vague and incomplete. The same basic obstacle effects curative therapy, for cure of disease is predicated upon eradication of the causes thereof. Furthermore, cure is obstructed by the diminution of the capacity of the senescent organism to repair itself after injury.[6] Palliative therapy seeks merely to conceal distressing symptoms in otherwise hopeless situations. It would be discouraging indeed if palliative treatment were the only type from which geriatric medicine could hope to get results.

A less clearly appreciated objective is control. Control is not cure, nor is it mere palliation. Control is the type of therapy applied in diabetes mellitus, hypertensive arterial disease, arteriosclerosis, myxedema, pernicious anemia, gout and the climacterium. The controlled diabetic still has diabetes, but he is physiologically well. Frequently, but not invariably, control of chronic and progressive disease is accomplished by replacement therapy. It is curious that the adjective "controlative" is not in the dictionary. It should be. Its meaning is surely clear to all. "Controlative" therapy seeks not only to reëstablish homeostasis disturbed by disease, but also to *retard progression.* Senescence per se, and most of the chronic and progressive disorders of later years, are not amenable to cure. They are, however, amenable to control and retardation. This is the form of therapy most appropriate to the majority of the problems of geriatric medicine.

One more therapeutic objective must be considered: *constructive therapy.* There has been little of this applied to adults, but pediatricians have taken apparently well babies and made them healthier by scientific feeding and meticulous attention to hygiene and immunity. These healthier children become healthier adults. Similarly geriatrics has the opportunity to modify and retard the detrimental consequences of senescence. Health is relative, never absolute. There is always room for improvement. Treatment of

disease is a "reconstructive" function. It is suggested that treatment of the apparently well, to raise health closer to an optimum, be called "constructive therapy." Not only does this newly applied term adequately define the objective, but it may also serve another useful purpose in diminishing the resistance of men and women to what has been called loosely "preventive medicine." To the average mind prevention implies prohibition and irksome restrictions to avoid something which, with luck, may be escaped anyway. Prevention has a negative connotation. Construction is positive. Constructing health rather than merely preventing illness follows the ancient axiom of war: Attack is the best defense.

The potentialities of constructive and "controlative" therapy for adults are immense. Conscientious application of existing knowledge in such fields as nutrition, endocrinology, hematology and psychiatry can do much to increase well being during senescence. Such guidance, however, *must be applied individually.* The wholesale methods of public health are decidedly inadequate for older age groups. The method of the wholesale approach has been directed toward keeping sources of injury away from the individual. No improvement in the intrinsic vigor, resistance and endurance of the individual can be expected from these methods. Sanitation, quarantine and mass immunization have brought about a brilliant reduction in morbidity and mortality from infective diseases. Thus the major benefit has been with the young. These measures have no effect upon the incidence, disability and mortality from degenerative disorders such as cardiovascular disease, arthritis, diabetes mellitus, anemia, gout or cancer. These latter major sources of illness in later years are endogenous. Protection from external menace will not prevent them.

Constructive or preventive medicine for adults must deal with people individually. With age comes increasing divergence among individuals. Individuality may be defined as the composite of the physical, mental and functional attributes congenitally inherited and modified by the innumerable intoxications, fatigues, infections, psychic and physical traumata which constitute the vicissitudes of existence. It is these latter modifying factors which vary markedly. No two persons live identical lives.

The keystone of the arch of geriatric medicine is the *periodic health inventory.* The bridge heads are thoroughness and individualization in diagnosis and, especially, management. Such inventories should be more than merely examinations to rule out florid disease. Health evaluation must include clinical studies to measure functional reserve capacities. Early detection of depreciation of functional capacities permits of wise counsel to protect the senescing or injured structure at a time when rest, proper nutrition, correction of anemia, and other items may accomplish the most in prolonging relative health. The value of such periodic audits depends upon the quality of the advice. A complete diagnostic study merely recorded on the clinical record does the patient little good. Diagnosis exists for the purpose

of treatment, whether it be reconstructive therapy for disease or constructive therapy to make health more nearly optimal.

There are many obstacles to the accomplishment of these objectives. They are serious, but not insurmountable. Expense is the first difficulty. Health mensuration requires time for functional study and the highest type of diagnostic acumen. Secondly, clinicians are sadly handicapped by lack of clinical methods for measuring many functional reserves and also by inadequate data as to what constitutes normality in relation to age. There is urgent need for research along both these lines. The criteria of health vary with age. Thirdly, there has been an unfortunate lack of appreciation of the potentialities of preventive geriatrics [7] on the part of physicians. And last, but not least, is the obstacle arising from the fact that the initiative for such constructive guidance must be taken by the patient. Perhaps a major reason why public health has been so effective is that its methods demanded no effort on the part of the beneficiaries of the blessings of sanitation. The older person seeking to maintain health *must* exert himself on his own behalf. There is an immense inertia against prophylaxis of any type. The benefits of prevention are demonstrable only statistically and statistics have little emotional appeal. However, constantly reiterated educational efforts can convert this paralyzing inertia into creative momentum. Pediatrics is having less and less difficulty in applying the principles of constructive therapy.

At this time of stress, when greed and hate threaten the very existence of our culture and military activity takes rightful precedence over all else, it may seem incongruous to emphasize the importance of geriatrics and to urge that more attention be paid to the health of those past the meridian. But defense, like therapeutics, is more than heroic attack upon exogenous menaces, no matter how vital that may be. Defense must consider the internal milieu of the body politic as medicine is attentive to the homeostatic mechanisms of the sick organism. The equilibrium of the nation is disturbed by the shifting balance of our population. This shift may prove wondrously advantageous if increased longevity is paralleled by health and productiveness. It may become disastrous if the chronic, progressive and disabling disorders of later maturity are not controlled. Not infrequently the most precarious period of an illness is *after* the crisis. We must see ahead and become better prepared to cope with the problems of senescence through research and more conscientious clinical application of existing knowledge.

Even in the immediate present geriatrics is urgently significant. Industry is becoming aware of the increasing importance of the older worker.[8] Experienced, skilled men are needed; young men are going into military service. There is great need for objective data concerning such problems as changes in capacities which come with aging, relation of age to fatigue, the effects of specific occupations in exacerbating chronic disease, criteria of physical and mental fitness in later years, and many more.

Furthermore, the leaders in all fields of endeavor are older men. Wisdom is conditioned by experience, which is a factor of time, or age. Aging does *not create* critical judgment, but fosters its growth when intelligence exists in youth. The young fool will become the old fool, should he live long enough; but the bright lad should become a usefully wise old man. Aging fixes and intensifies character. Understanding thinkers become increasingly tolerant and wise, the sanctimonious become opinionated bigots. The decisions of older men guide the national destiny. Special knowledge, trained judgment, and experience make many elderly men almost irreplaceable. The tragedy of premature disability, death or forced retirement of a wise leader is not a personal one; it is a loss to the nation of judgment which can be replaced only by years of experience. The added stresses of the present emergency are added menaces to health. The conservation of the health and effectiveness of older men in posts of grave responsibility is a major obligation of medical science, an obligation not primarily to the individuals themselves, but to the Nation and our culture.

Every privilege entails equivalent responsibility. Failure to conform to this law of nature has caused the decline and fall of many cultures. It is so easy for the individual to accept privilege that before long it is taken for granted as an inalienable right. We have no right to freedom unless we struggle for it, we have no right to health without effort on our part. The privilege of longevity entails the obligation of endeavor to prevent long and premature disability. Individual effort to maintain health and continued usefulness into late senescence is a duty to the community. As the youth prepares to become an adult, so should the adult prepare for senescence and senility. The time to start application of constructive medicine in late maturity is *now.*

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CASE REPORTS

ACUTE THROMBOCYTOPENIC PURPURA HEMORRHAGICA WITH LYMPHOCYTOSIS; REPORT OF A CASE *

By Morris Tager, M.D., and Kalmen A. Klinghoffer, M.D.,
New Haven, Connecticut

In 1936, Minot presented three cases of acute thrombocytopenic purpura hemorrhagica with lymphocytosis,[1] and three related cases of intermittent purpura associated with menstruation. No further cases of this nature have been reported, although a fourth one, unassociated with menstruation, has been seen by Minot [2] since 1936. In view of the difficulty of early diagnosis and the importance of prompt recognition of this dyscrasia, it was deemed of interest to present the following case.

Case Report

The patient, a 20-year-old, single, white, female law student, was admitted to the New Haven Hospital on October 6, 1938. She had been in excellent health until 24 hours before hospitalization, when she first noted several small red spots on her face, tongue, and buccal mucosae, her attention having been called to the latter by slight gingival bleeding. These manifestations were not associated with any local or general discomfort, although there had been a sensation of some blood trickling from time to time in the nasopharynx. During the night, however, she became dizzy, apprehensive, and experienced several chills, without any actual rigor. She attempted to rise to seek aid, lost consciousness momentarily, and fell, bruising her right elbow. She recalled nothing further except that she perspired freely during the rest of the night. On the morning of October 6 she noted many new purpuric lesions scattered over her body, especially on the feet. There was no headache nor other pain, no obvious bleeding from the gastrointestinal or genitourinary tract. The last menstrual period had occurred some two weeks prior to this acute episode and was in no way remarkable. There was no history of any recent acute infection, no known exposure to chemicals, no intake of drugs other than rarely an aspirin tablet, and no dietary deficiency. The patient had no known contact with anyone presenting similar lesions. The past history was negative for any hemorrhagic phenomena and was otherwise not remarkable, except for some evidence pointing to allergy in that she had had mild symptoms of hay fever for five years and an isolated instance of strawberry sensitivity some 10 years previously. There was no family history of blood dyscrasia, and the remainder of the history was non-contributory.

Physical examination upon admission revealed a well developed and nourished girl of 20, coöperative and alert, and not appearing chronically or even acutely ill. There was no pallor nor icterus. The temperature was 101° F. (rectally), pulse 80, respirations 20, and the blood pressure 120 mm. Hg systolic and 80 mm. diastolic. Complete physical examination, excepting the purpura, showed nothing remarkable.

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From the Department of Internal Medicine, Yale University School of Medicine, and the Medical Service of the New Haven Hospital, New Haven, Conn.

Worthy of special note was the absence of splenomegaly, lymphadenopathy, and evidence of significant internal bleeding. Scattered over the face, palate, and lower extremities were numerous petechiae of varying size. Except for a large ecchymosis of the right elbow, the site of injury during the preceding night, the upper extremities and trunk were largely spared. On the lips, tongue, and gums were purplish-red lesions with elevated borders and several millimeters in diameter, presumably secondary to the extravasation of blood. The gums were otherwise not spongy or swollen. There were no splinter hemorrhages under the finger nails.

Laboratory Findings. Although the urine was clear on admission, it became grossly bloody within 12 hours, but reverted to normal by the eighth hospital day. Similarly, the stools which became grossly bloody 48 hours after admission, and subsequently became tarry, were free of gross and microscopic blood by the eighth hospital day.

The non-protein nitrogen was 24 mg. per cent, icteric index 7, Kahn reaction negative. Blood culture showed no growth. Stereoscopic roentgenogram of the chest revealed no abnormality.

On the day of admission, October 6, 1938, the coagulation time in three successive tubes was 15, 18 and 20 minutes respectively (test tube method), and the clot failed to retract in 24 hours. The bleeding time (Duke's method) was over 24 minutes. On October 17, 1938, the eleventh hospital day, although the coagulation time was normal, the clot still failed to retract in 24 hours, and the bleeding time was 10 minutes. By October 26, 1938, no abnormalities were detectable in any of these tests.

On admission the capillary fragility test, performed by maintaining the blood pressure cuff for five minutes at 110 mm. of mercury, was strongly positive, over 100 petechiae being present in a 2½ cm. circle.

The sheep cell agglutinations were as follows:

October 6, 1938—1 : 32 absorbed by guinea pig kidney
October 17, 1938—1 : 16
December 24, 1938—1 : 2

In table 1 selected blood counts are presented with the differentials limited to the cells of particular interest for this case. It will be noted that the admission red blood count and Sahli hemoglobin were within normal limits, but dropped to a low of 3.1 million and 55 per cent hemoglobin during the period of severe blood loss of the first week of hospitalization. A few normoblasts were noted during this period, but they were not in evidence subsequently. The red cells showed no other abnormality on smear nor when the various cell indices were calculated. The red cell counts and hemoglobin values were normal by the ninth hospital day.

The total white cell count was characterized by a moderate elevation during the first four days, followed by normal subsequent values. The neutropenia on admission was succeeded by a gradual rise in the granulocyte series, associated with a shift to the left persisting from the eighth to the thirtieth day of illness. Of the "normal" lymphocytes, there was a higher proportion of large cells than is ordinarily found. The eosinophiles, basophiles, and monocytes were within normal limits, or unnoted.

The distinctively abnormal features consisted in the presence of "pathological cells" and the striking reduction of platelets.

The "pathological cells" were largely atypical, young mononuclear cells of varying sizes, shapes, and staining reactions, with predominantly non-granular, well-staining blue cytoplasm and leptochromatic nuclei. Some were not unlike the cells encountered in infectious mononucleosis; a few were indistinguishable from 'blasts. These cells reached a peak of 68 per cent of the total on the seventh hospital day, and were occasionally encountered as late as 70 days after the onset of the illness.

Platelets were completely absent from the smears during the first four days, but appeared, though greatly diminished, by the fifth day. The counts, listed in table 1, demonstrate the persisting depression of platelets for some three weeks, following which a return to normal took place.

Clinical Course. The patient's temperature fluctuated between 99° and 101° F. during the first week, but was not elevated thereafter except for an occasional rise to 99.6° F. She was placed on strict bed rest, and in view of the normal admission red blood cell count and hemoglobin level and the presumptive diagnosis of acute leukemia, transfusion was withheld during the first 24 hours. However, with the progression of the purpura, notably an increase in cutaneous petechiae, gingival bleeding, the appearance of hematuria and melena, and the consequent development of anemia, a series of small transfusions (table 1) was administered. The clinical course was rapidly

TABLE I

Illness Day	R.B.C.	Hgb. % Sahli	Total W.B.C.	Pmn. % Seg.	Pmn. % Non-Seg.	Lymph. Normal	Pathol. Cells	Platelets	Transfusions c.c.
1									
2*	4.5	86	14,880	6	4	55	35	0†	
3	4.7	88	11,600	6	2	24	66	0‡	250
4								+‡	250
5	4.6	78	13,750	14	7	13	66		
6									125
7	3.3	59	6,900	19	9	12	60		300
8	3.1	55	5,700	18	6	8	68		300
9	3.5	72	7,500	16	16	28	40		300
10	4.0	81	7,550	15	8	32	44		
12								15,000	
13	4.3	82	5,800	13	18	48	15		
16	4.0	75	5,550	15	20	48	17		
19								43,000	
22	4.0	82	5,650	21	21	42	12		
23								75,000	
27†	4.2	82	6,600	23	27	43	4	185,000	
31	4.0	75	8,100	37	15	40	2	300,000	
38								700,000	
71	4.1	81	6,600	44	10	42	1		
99	3.9	81	7,200	44	5	38	0		
178	3.9	78	6,200	41	4	44	0		
255	4.2	81	9,400	40	3	52			

* First hospital day.
† Day of discharge from hospital.
‡ Smear observations.

favorable, with the hematuria and melena no longer present by the eighth hospital day, and all cutaneous manifestations of purpura absent by the fourteenth day. No new physical findings appeared and the patient was discharged on October 31, 1938, to convalesce further at home. During the following eight months she returned for frequent hematological and physical examinations. Except for the persistence of a few pathological cells until the seventieth day, nothing significantly abnormal was encountered clinically or hematologically. To the present time, some two and one-half years after the acute episode, the patient has remained completely well.

DISCUSSION

The diagnosis on admission to the hospital presented considerable difficulty. It was the consensus of all observers that acute leukemia was most likely, the

coexistence of a strikingly pathological blood smear and profound thrombopenia with purpura hemorrhagica making this diagnosis a virtual certainty. However, it was equally evident that the nature of the abnormal cells was obscure, and that they were difficult to classify on the basis of present knowledge of cell morphology. The futility of basing a definitive diagnosis on the morphology of the cells alone becomes apparent from the conflicting opinions of several well qualified authorities in various centers to whom the smears were submitted. Indeed, acute myelogenous, lymphatic, and monocytic leukemias were all suggested, the latter on the basis of supravital studies. A later opinion, which had the advantage of knowledge of the favorable progress of the case, was acute toxic injury to the hematopoietic tissues.

The appearance of some of the cells also raised the possibility of infectious mononucleosis. Thrombocytopenic purpura, however, is extremely rare in this disease, and the total absence of the usual clinical features, as well as significant elevation of sheep cell agglutinins, eliminated it as a diagnostic possibility. Although the absence of leukocytosis, lymphadenopathy, and splenomegaly is not incompatible with the diagnosis of acute leukemia, the absence of anemia in the presence of well marked thrombocytopenic purpura is most unusual, and might well have raised some doubts as to the correctness of such an interpretation.

Dr. William Dameshek, who was among those consulted, suggested that the present case might fall in the category described by Minot. Although admitting that statistically it was all but a 100 per cent chance that the occurrence of a very marked lymphatic reaction in association with the absence of blood platelets pointed to acute leukemia, he was impressed by the paucity of true blasts, and interpreted the morphologically dominant cell as representing abnormal lymphocytes of varying sizes, shapes, and staining reactions.

It is evident that this view is probably correct. This case shares with Minot's first three cases the diagnostic features of sudden appearance of hemorrhagic phenomena, profound thrombocytopenia, abnormal lymphocytosis, absence of initial anemia, favorable response to transfusion, and ultimate recovery.

The prognosis of this dyscrasia, unassociated with menstruation, is excellent. Although Minot's third case, that of the 10 year old girl, has been lost track of, he has been able to follow his first two cases, both males, for totals of six and nine years respectively, without any evidence of recurrence.[2] The present case has remained entirely well during the past two and one-half years.

Since all reported cases have received blood transfusions, it is obviously impossible to be entirely certain whether the untreated patient suffering from this disease might not recover spontaneously without such therapy. The risks of irreversible damage to vital organs in the course of a virtually total thrombocytopenia are, however, too well known to allow a patient to go without benefit of such therapy. The danger to the patient of a failure to recognize this dyscrasia, therefore, lies chiefly in regarding it either as a case of acute leukemia, in which, in the absence of anemia, transfusions might be considered elective rather than imperative, or as a case of idiopathic thrombocytopenic purpura hemorrhagica requiring splenectomy.

No clues are at hand as to the etiology or pathogenesis of this disease. Detailed inquiry as to any possible infectious, allergic, or chemical antecedents, failed to bring to light any likely incitant.

SUMMARY

A case of acute thrombocytopenic purpura hemorrhagica with abnormal lymphocytosis occurring in a 20 year old white female is presented. It was characterized by the sudden appearance of hemorrhagic phenomena in the absence of initial anemia, profound thrombocytopenia, "abnormal" lymphocytosis, favorable clinical course following blood transfusions, and no recurrences during the follow-up period of two and one-half years.

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STUDIES ON THE EFFECT OF MASSIVE QUANTITIES OF SODIUM BICARBONATE ON THE ACID BASE EQUILIBRIUM AND ON RENAL FUNCTION

REPORT OF A CASE WITH REMARKABLE TOLERANCE*

By JOSEPH B. KIRSNER, M.D., Ph.D., and WALTER LINCOLN PALMER, M.D., Ph.D., F.A.C.P., *Chicago, Illinois*

INTRODUCTION

ALTHOUGH considerable emphasis has been placed on the development of alkalosis during the alkali treatment of peptic ulcer, this complication does not occur in most patients so treated. Recent studies [1] have indicated that therapy may be continued for many years without significant alteration either in the acid base balance or in renal function. Berger,[2] Jeghers and Lerner,[3] and others occasionally have observed patients in whom the prolonged use of large quantities of sodium bicarbonate and calcium carbonate caused no apparent untoward effects. This remarkable tolerance to alkalis is particularly well illustrated by the following case in which the ingestion of the enormous quantity of 32,000 grams of sodium bicarbonate in 20 months produced only minimal changes in the acid base equilibrium and no demonstrable decrease in the urea clearance.

CASE REPORT

E. L. R., a 23-year-old unemployed shipping clerk, had experienced ulcer distress for five years, during which time hospitalization had been required on two occasions because of massive hemorrhage. Alkalosis was said to have been present on one occasion as a result of the excessive ingestion of alkali following the appearance of tarry stools. This happened one year before his admission to the University clinics. Physical examination at the time of admission was negative except for localized tenderness in the epigastrium. Roentgen studies disclosed a stenosing duodenal ulcer with a

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From the Frank Billings Medical Clinic, the Department of Medicine, University of Chicago.

crater measuring 15 mm. in diameter. The patient was observed in the hospital for 11 months (September 3, 1938, to August 1, 1939) and subsequently in the University clinics until November 13, 1940, a total period of 27 months. The method of study was as follows:

No alkali was administered for several days. Control determinations were made of the serum CO_2, pH and chloride, and of the blood urea nitrogen.[4] Renal function was estimated by several urine concentration tests and by the urea clearance test of Van Slyke.[5] These studies were repeated at least twice each week during the period of hospitalization and at less frequent intervals in the Out-Patient Department. Occasional measurements were made also of the total base[6] in the serum. The fluid intake and output were recorded daily for nine months of the hospital stay. The daily protein content of the diet was estimated during the entire study because a low protein intake may be accompanied by a depression of the urea clearance despite normal renal function.

Diet—Protein Intake. The basic diet in the hospital consisted of 90 c.c. of equal parts of milk and cream taken at hourly intervals from 7 a.m. to 7 p.m. Feedings consisting of soft bland foods were added gradually so that after four weeks the patient received a modified three meal ulcer diet with hourly milk and cream. After discharge from the hospital the quantity of milk and cream was decreased and the three

TABLE I

Month Year	Avg. Daily Fluid Intake	Avg. Daily Urinary Output	Gastric Aspiration	
			Avg. Daily Amount	No. of Days Aspirated
Nov. 1938	3,478 c.c.	2,458 c.c.	388 c.c.	10
Dec. "	3,253	2,539	347	27
Jan. 1939	3,718	2,923	282	22
Feb. "	5,011	3,936	228	28
Mar. "	4,951	3,378	188	29
Apr. "	4,588	3,377	143	25
May "	4,326	2,650		
June "	4,422	2,780		
July "	3,446	1,792		

meal program enlarged. The protein intake, although somewhat reduced during the initial four to six weeks, was consistently above basal requirements, averaging 55 grams daily for the first month (September 3 to 30, 1938), 77 grams during the second month (October 1 to 31, 1938), and 102 grams daily between November 1 and 30, 1938. The protein intake during December (December 1 to 31, 1938) averaged 88 grams per day and was maintained at approximately this level for the remainder of the study.

Fluid Balance. The fluid intake and output were measured daily between November, 1938, and August, 1939, and are recorded as averages per day during each month in table 1. The large quantities of alkali administered precluded occasional efforts to reduce the 24 hour fluid intake below 3000 c.c. The gastric contents were aspirated nightly for a period of six months (November, 1938, to April, 1939). The quantities removed varied widely, ranging from 30 to 950 c.c.; the average daily amounts withdrawn are noted in table 1. It will be observed that the volume of aspirate per day gradually decreased from an average of 388 c.c. in November, 1938, to 143 c.c. in April, 1939.

Alkali Therapy. This was begun several days after admission to the hospital and continued for 20 months; the intake per month is shown in the chart. Between September 6, 1938 and September 30, 1938, the patient received 135 grams of sodium bicarbonate, 219 grams of calcium carbonate and 352 c.c. of aluminum hydroxide.

During October 1938, 48 c.c. of aluminum hydroxide, 302 grams of calcium carbonate, and 830 grams of sodium bicarbonate were given. Massive quantities of sodium bicarbonate were administered between November 1, 1938, and April 22, 1940. The daily intake averaged 90 grams for the eight month period between November 1, 1938, and August 1, 1939. The quantity of alkali was then gradually reduced to 60 grams daily between August 1, 1939, and December 1, 1939, and for the five month period between December 1, 1939, and April 22, 1940, averaged approximately 30 grams per

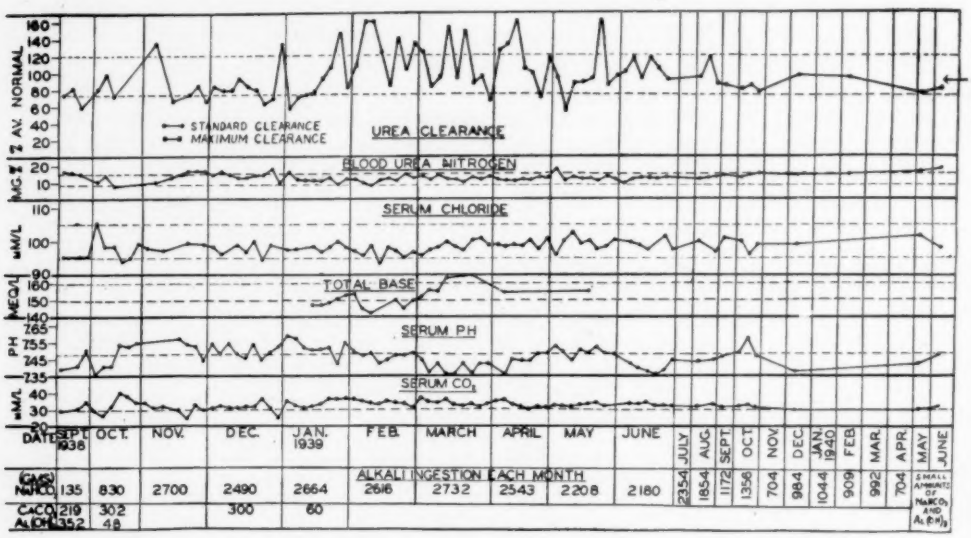

FIG. 1. Serum electrolytes and urea clearance during continued sodium bicarbonate administration.

day. The total amount of alkali administered during the 20 months between September 6, 1938, and April 22, 1940, consisted of 400 c.c. of aluminum hydroxide, 881 grams of calcium carbonate and 31,414 grams of sodium bicarbonate. Alkalis were taken only occasionally during the final seven months (April 23, 1940, to November 13, 1940), and the intake was comparatively small.

Routine Laboratory Data and Clinical Course. The red and white blood cell counts and the hemoglobin remained within normal limits. Three histamine tests (0.6, 0.6, 0.65 mg.) disclosed a maximum free acidity of 118, 110, and 150 clinical units respectively. Forty-five urine specimens were examined; the specific gravity varied from 1.015 to 1.034, averaging 1.024; the reaction was constantly alkaline: a trace of albumin was detected on four occasions. Numerous electrocardiograms revealed no significant changes. The patient's clinical course was entirely uneventful. His body weight gradually increased from 54 kg. to 66 kg. during the 27 month period of observation. The ulcer crater disappeared in five weeks and did not reappear.

Acid Base Balance. The acid base balance was determined 78 times during the present study (see chart). The serum CO_2 during the period of hospitalization varied usually from 31 to 35 mM/L (normal 20–30 mM/L) with increases to 37.7 and 39.2 mM/L on two occasions. After discharge from the hospital (August 1, 1939, to November 13, 1940) the CO_2 remained within normal limits. The serum pH paralleled the CO_2 and fluctuated usually from 7.33 to 7.50 (normal 7.35 to 7.45), although values between 7.50 and 7.53 were noted frequently. The total base was determined on 18 occasions; only two of the results (163.4 and 164.9) exceeded

the normal range of 150 to 160 milliequivalents per liter. The serum chloride was consistently within the normal limits of 95 to 105 millimols per liter.

Renal Function. Two urine concentration tests before alkali therapy revealed maximum specific gravities of 1.025 and 1.027. Three urea clearance tests during the control period measured 60, 75 and 80 per cent of average normal respectively (lower limit of normal considered to be 75 per cent). The urea clearance subsequently was determined on 75 occasions in the succeeding 27 months; 30 of these were by the standard clearance with urine volumes never less than 1 c.c. per minute. Forty-five of the determinations were by the maximum clearance; the urine volumes varied from 2.1 to 9.2 c.c. per minute. The urea clearance was below 75 per cent on 10 occasions; the other 65 clearances fluctuated within the normal range of 75 to 150 per cent. It is of interest to note that the two final clearances of 75 and 80 per cent, after the administration of 33,000 grams of alkali, duplicated exactly the values obtained before alkali therapy.

Blood Urea Nitrogen. The blood urea nitrogen remained normal throughout the entire study. The results ranged from 8.2 to 16.5 mg. per cent with an average of 11 to 12 mg. per cent.

Comment

The administration of large quantities of sodium bicarbonate results usually in an elevation of the serum CO_2 and a corresponding secondary reduction of the serum chloride. The urinary excretion of the titratable acid plus ammonia falls while the bicarbonate content and pH of the urine rise. Palmer and Van Slyke [7] found that following the administration of sodium bicarbonate the plasma bicarbonate of patients with nephritis often rose considerably higher than the level seen in normal individuals before the urine became alkaline. Ellis [8] observed a definite bicarbonate excess and a high serum pH in a nephritic patient with acid urine, and others [9, 10] have reported similar findings. Alkalosis following the ingestion of sodium bicarbonate apparently represents merely a retarded excretion of bicarbonate. The remarkable tolerance to sodium bicarbonate exhibited by our patient may be attributed, therefore, to the excellent function and reserve capacity of the kidney, as well as to the large volume of fluid available for excretion of the alkali.

The absence of demonstrable renal injury after the administration of massive quantities of sodium bicarbonate in this patient is in accord with recent clinical observations indicating that alkalis per se do not cause intrinsic renal disease. The fact that alkali therapy may be continued for years without permanent depression of the urea clearance has been mentioned previously. Evidence likewise has been obtained suggesting that hypochloremia and dehydration may be of great etiologic importance in the development of alkalosis.[11] The impairment of renal function observed during alkalosis usually disappears promptly after correction of the acid base disturbance. The rapidity with which renal efficiency may be restored indicates that no intrinsic injury to the kidney occurred, an observation which gains further support by the failure of Hoag et al.[12] to observe anatomic changes in the kidney of the experimental animal after the subcutaneous and intravenous injection of therapeutic doses of sodium bicarbonate. Kirsner [13] administered massive quantities of sodium bicarbonate both orally and intravenously to a series of dogs for as long as nine months without producing any significant morphologic changes in the kidney, even though alkalosis had been induced repeatedly. It is obvious from these studies that the

normal kidney can cope successfully with excesses of alkali for a prolonged time without untoward effects provided adequate amounts of fluid and of salt are available.

Summary

The administration of 32,000 grams of sodium bicarbonate in 20 months to a patient with normal renal function produced no marked alteration in the acid-base balance and no decrease in the urea clearance.

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EXFOLIATIVE DERMATITIS DUE TO PHENOBARBITAL: REPORT OF A CASE WITH RECOVERY *

By Sherwood W. Barefoot, M.D., and J. Lamar Callaway, M.D.,
Durham, North Carolina

Since their introduction for clinical use in 1913, the barbiturates have found an increasingly prominent and deserved place among the commonly used sedatives. The increasing number of reports during recent years regarding their toxic reactions is an indication of their popularity.

The incidence of toxic reactions due to the barbituric acid derivatives varies considerably in different hands. Fifteen years after their introduction Menninger,[1] after a thorough review of the literature, was able to find only 41 instances of cutaneous eruptions attributed to barbiturates. To this list, he added three of his own cases. In 1927 Jackson [2] reported six instances of skin rash in a series of 500 patients treated with phenobarbital. Contrasted with these low figures, Scarlett and MacNab,[3] in 1935, stated that they encountered such frequent toxic reactions from phenobarbital that they were no longer using the drug except in instances of severe convulsive seizures.

In the Duke Hospital Clinic cutaneous manifestations of toxicity from barbiturates have been rare, and this report deals with the only recognized instance of any clinical consequence. In the Duke Clinic, when prolonged administration of a sedative is desired, barbiturates are generally given preference over bromides since the toxic reactions from the former have been much less in evidence than the disturbing mental symptoms produced by the prolonged ingestion of bromides.[4]

It is now common knowledge that the administration of barbiturates may be followed by a dermatitis medicamentosa which usually subsides promptly when the drug is withdrawn. The occurrence of exfoliative dermatitis following the ingestion of barbiturates, however, is so rare that these drugs have not in the past been considered as an important etiological factor. The incidence of such occurrences, when compared with the number of persons receiving these drugs is, certainly, extremely small. When such a reaction occurs it is of grave significance, since it is accompanied by severe systemic manifestations, and the majority of such patients do not recover. It is, therefore, important that physicians be acquainted with the fact that barbituric acid derivatives may produce such serious consequences.

In all cases of exfoliative dermatitis of obscure origin in which the onset was preceded by the ingestion of barbiturates or drugs of obscure origin, it would seem advisable to use a sedative not derived from barbituric acid, since in such instances one may be dealing with a case in which one of the barbiturates is the etiological agent.

In 1919 Hueber [5] described a fatal case of "chronic infiltrating desquamating eczema covering the whole body, palms and soles" following the administration of phenobarbital. This may have represented a case of exfoliative dermatitis, but credit for first reporting a case of exfoliative dermatitis due to phenobarbital

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From the Section of Dermatology and Syphilology of the Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

is given to Hamilton, Geiger, and Roth.[6] In 1926 they described a case in which there was loss of the integument including the finger and toe nails as well as part of the hair. Their patient recovered after a prolonged illness. In 1927 Jackson [2] reported a case of generalized desquamation, but the desquamation was preceded by vesiculation. We are not accepting this patient as an instance of exfoliative dermatitis, since only those cases in which the appearance was that of an arsenical exfoliative dermatitis, as was the case in our patient, are included. In 1929 Chavany and Vannier [7] reported two cases with fatal outcome, and Poole [8] described a case with death. In 1932 Lancaster [9] reported an instance similar to ours in that exfoliative dermatitis followed the ingestion of phenobarbital on two different occasions, and was followed by complete recovery in each instance. Millard [10] in 1933 reported an instance of universal exfoliative dermatitis with a fatal termination following the administration of phenobarbital. In 1934 Haubrick [11] described a case of exfoliative dermatitis following the ingestion of phenobarbital with recovery. In 1935 Hickmann [12] described a case of generalized exfoliation including the hair with a fatal outcome; and in Canada Scarlett and MacNab [3] reported the sixth fatal case attributed to phenobarbital. There was generalized desquamation but here, again, the exfoliation was preceded by a bullous eruption and we are not including this as a case of exfoliative dermatitis. A fatal case of exfoliative dermatitis following the administration of phenobarbital was presented by Sweitzer and Layman [13] in 1937. Wile and Benson [14] in 1940 reported two fatal cases. The most recent reports were made by Sexton, Pike, and Nielson [15] in February 1941 in which they described one fatal case, and by Winer and Baer [16] in 1941 who reported a fatal case of exfoliative dermatitis due to phenobarbital with clinical and postmorten studies.

In the literature we have found 13 cases which appear to have been examples of true exfoliative dermatitis following the ingestion of barbiturates, and in 10 of these the outcome was fatal. We are reporting a single instance with recovery. In this patient the etiological diagnosis seems definitely established since, on two occasions, the ingestion of phenobarbital was followed by an exfoliative dermatitis.

Case Report

Mrs. I. B., a 58-year-old white housewife, was admitted to Duke Hospital on April 4, 1940. Her complaint was desquamating dermatitis with onset 10 days previously. There were no pertinent findings in her family history, and there was no history of allergy. Marital history was non-contributory.

The patient's general health had been good until 10 years previously, at which time she developed a right hemiplegia following a severe epistaxis. The paralysis cleared up without residual symptoms within a few months. She had experienced an uneventful menopause five years previously. No allergy nor known idiosyncrasies were present. Five months prior to admission she had been ill with "flu" and had not felt as well as usual since that time, having complained of weakness and nervousness. A review of the dietary history revealed a low protein intake.

Ten days prior to admission, the patient noticed that her face seemed to be sunburned, and on the following day there was erythema of the entire body. She consulted her physician who advised her to discontinue the 0.032 gr. tablets of phenobarbital three times daily which he had prescribed five days previously and gave her

soothing lotions to apply locally. Severe generalized pruritus developed, and within two or three days after the onset there was considerable exfoliation and the corners of the mouth and palms became fissured.

Physical examination revealed temperature to be 38.4° C., pulse 95, respirations 20, blood pressure 160 mm. Hg systolic and 84 mm. diastolic. The patient was a moderately obese white female in obvious discomfort and complaining of chilliness. There was generalized erythema with thickening of the skin over the face and extremities. The skin of the palms was greatly thickened, and the palms and corners of the mouth were fissured. The scalp showed considerable scaling. There was no lymphadenopathy. The tongue showed atrophic papillae. There were several carious teeth and considerable peridental infection. The tonsils showed evidence of chronic infection. The lungs were clear. The heart was not enlarged and auscultation was negative except for a soft apical systolic murmur. The peripheral vessels showed moderately advanced arteriosclerosis. Abdominal, pelvic, and rectal examinations were negative. There was slight pitting edema of both ankles (note low serum proteins). Neurological examination was negative except for slight impairment of vibratory perception below the knees.

Accessory Clinical Findings. Hemoglobin 12.4 grams (Sahli) or 80 per cent. Red blood cells 3,650,000 cells per cubic millimeter. White blood cells 9,600 cells per cubic millimeter. Differential count: Polymorphonuclears 65 per cent, lymphocytes 13 per cent, monocytes 3 per cent, eosinophiles 17 per cent, basophiles 2 per cent. Smear of the peripheral blood was not remarkable. Sedimentation rate 5 millimeters per hour, corrected (normal). Urine negative on repeated examinations, and a catheterized specimen was sterile on culture. A 24 hour urine specimen was negative for arsenic. Stool was negative for parasites and blood, and on culture showed no unusual organisms except for a few colonies of hemolytic *E. coli.* Blood culture was sterile. Throat culture showed colonies of non-hemolytic *Staphylococcus aureus* and alpha streptococci. Culture of bile removed by duodenal intubation was sterile. Studies of the fasting gastric contents showed the presence of a normal amount of free hydrochloric acid. Chemical analysis of the blood showed the following findings: non-protein nitrogen 29 mg. per cent, fasting sugar 82 mg. per cent, plasma chlorides 608 mg. per cent, total serum proteins 4.6 grams per cent, albumin 2.8 grams per cent, globulin 1.8 grams per cent. The albumin-globulin ratio was lowered, being 1.5. Roentgenogram of the chest showed widening and tortuosity of the aorta, but the heart was of normal size and shape. The lungs appeared to be normal. Plain roentgenogram of the abdomen showed no visceral abnormalities. The lumbar spine exhibited considerable hypertrophic arthritic changes. Oral cholecystogram showed normal filling and emptying of the gall-bladder. Roentgenograms of the sinuses were negative. Electrocardiogram showed no changes indicative of myocardial disease.

Course in the Hospital. During the first week in the hospital, the patient had a low grade fever which was seldom above 38° C. After the first week, the temperature was normal. By the end of the first hospital week the skin over the entire body was exfoliating. After another week the exfoliation practically subsided and the skin gradually assumed a normal appearance.

Approximately one week after admission the patient developed a mild bilateral conjunctivitis, which was treated with the instillation of a 2 per cent solution of boric acid and subsided within a period of 10 days.

Local treatment to the skin consisted of starch baths and soothing lotions containing large amounts of olive oil. Ten c.c. of a 10 per cent solution of calcium gluconate intravenously, and 10 c.c. of autogenous blood intramuscularly were administered on alternate days. She was also given concentrates of all the known vitamins as well as iron.

During the last week in the hospital the lower bicuspids and tricuspids were extracted, and a tonsillectomy and adenoidectomy were performed with no untoward results. The blood cytology remained essentially the same throughout the hospital stay with the eosinophilia gradually becoming less marked. The ankle edema, present on admission, subsided after the patient had been placed upon a dietary régime which included an adequate protein intake.

She was discharged May 9, 1940 with a diagnosis of exfoliative dermatitis of unknown origin. The cutaneous manifestations had completely subsided at the time of discharge.

Course after Discharge from Hospital. On June 4, 1940, about one month after discharge, the patient appeared in the Out Patient Clinic complaining of generalized pruritus. There was generalized erythema of the skin and the eyelids were edematous. She stated that the onset had occurred two days previously after she had taken 0.032 gram of phenobarbital on the preceding night. This was the first time that she had taken any barbiturate since leaving the hospital. With this information, we for the first time felt justified in attributing the previous episode to the ingestion of phenobarbital.

The patient has not been seen again since she lives at a distance of several hundred miles from Duke Hospital. We have, however, corresponded with her and in a communication dated June 28, 1940 she stated that following her visit to the Clinic the skin over the entire body had desquamated. She said that the sequence of the cutaneous manifestations had been identical with those of the previous episode, and that she had completely recovered.

Comment

Judging from the reports in the literature, and from our personal experience, the occurrence of exfoliative dermatitis following the administration of barbituric acid derivatives is quite rare. In our opinion, the causative agent in the case which we are reporting seems to be definitely established. The ingestion of phenobarbital on two different occasions was followed by an exfoliative dermatitis. Clinically, the cutaneous lesions could not be distinguished from an exfoliative dermatitis produced by arsenic. It is interesting to note that our case, as well as a good many of the reported cases, developed a conjunctivitis. This may be of some diagnostic value in as much as we have never seen this manifestation in a case of exfoliative dermatitis due to arsenic.

In the majority of the reported cases developing an exfoliative dermatitis following the ingestion of barbiturates, the outcome has been fatal. The gravity of the complication does not seem to be dependent upon the amount of the drug ingested. In our patient, the second episode followed the ingestion of only 0.032 gram of phenobarbital, whereas in other hands manifestations of serious complications did not appear until large amounts of the drug had been administered.

In the reports of the fatal cases of exfoliative dermatitis following the administration of barbiturates, no adequate explanation for the cause of death has been offered. Hueber's [5] case became uremic, but this seems to be an exception. Autopsies, when performed, have shown little other than terminal bronchopneumonia. Winer and Baer [16] found eosinophilia and severe vascular involvement of several internal organs, as well as tuberculoid structures in the spleen, in their case and felt that these tissue reactions were based on an allergic reaction.

Summary

1. In our experience, phenobarbital has proved to be a valuable sedative and toxic reactions have been very rare.

2. Barbituric acid derivatives, however, may be responsible for serious consequences including an exfoliative type of dermatitis which cannot, clinically, be distinguished from an exfoliative dermatitis produced by arsenic.

3. Patients with exfoliative dermatitis produced by barbiturates seem to have a tendency to develop conjunctivitis, which is quite rare in exfoliative dermatitis produced by other substances.

4. The prognosis in cases of exfoliative dermatitis due to barbiturates is grave and the systemic reactions are, as a rule, quite severe. In 12 previously reported cases, nine had a fatal outcome.

5. Clinical and postmortem studies have offered no satisfactory explanation in the majority of the fatal cases as to the cause of death.

6. The amount of barbituric acid derivatives ingested seems to have no relationship to the severity of the toxic reaction.

7. In treating patients with exfoliative dermatitis of obscure origin who give a history of ingestion of barbiturates or other preparations of unknown composition, it would seem advisable to use drugs other than barbituric acid derivatives for sedation.

8. A case of exfoliative dermatitis which has been thoroughly studied and in which the administration of phenobarbital on two different occasions was followed by exfoliative dermatitis is reported.

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POSTOPERATIVE PRECIPITATION OF VITAMIN DEFICIENCIES *

By MAX ELLENBERG, M.D., HENRY DOLGER, M.D., and HERBERT POLLACK, M.D., F.A.C.P., *New York, N. Y.*

PROLONGED chronic illnesses are often accompanied by anorexia and not infrequently by vomiting. In many instances, the nature of the illness may necessitate a restricted diet such as a low residue or bland diet for prolonged periods. By the time the patient enters the hospital he may, therefore, be in a state of partial vitamin depletion.

The preoperative preparation of the patient usually includes a sharply limited diet, especially when surgery of the gastrointestinal tract is contemplated. Preparation not infrequently includes the administration of intravenous fluids, adding the effect of an induced diuresis which would tend to deplete the body stores of the water soluble vitamins. Most parenteral fluids routinely contain glucose. The drain of a high carbohydrate metabolism on the vitamin B stores in the body has been recognized.

The insult of the operative trauma itself, as well as the deleterious effect of a prolonged anesthesia on the liver and other organs, would tend to disrupt the mechanism of the vitamin actions.

During the postoperative period, postanesthetic nausea and vomiting occur frequently. There is the necessity for complete restriction of food for a time; often after partial or total gastrectomy no food is given for days. The fluid balance is maintained by the long continued use of intravenous fluids which again usually contain glucose.

All the above enumerated factors add up on the debit side of nutritional balance and form a readily understandable background for the development of the observed vitamin deficiencies. The case herein presented fits into this picture very clearly.

CASE REPORT

K. U., a 75-year-old white male, was first admitted to the Mount Sinai Hospital in November 1938. For one year he had been suffering from epigastric pain unrelated to meals, constipation, loss of weight, and anorexia. A barium enema disclosed a stenosing lesion in the proximal portion of the transverse colon, having the appearance of a neoplasm. The patient refused operation and returned home. He was readmitted to the hospital in May 1940. In the intervening year and a half, he had had recurrent episodes of abdominal pain, progressively becoming more severe.

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From the Metabolism Clinics and the Surgical Services of The Mount Sinai Hospital, New York City.

Anorexia continued throughout this period and he lost an additional 20 pounds in weight. During the week immediately preceding this admission, he had had severe cramp-like abdominal pain and frequent, repeated vomiting. He presented the classical picture of subacute intestinal obstruction. A barium enema again revealed an obstructing lesion in the proximal portion of the transverse colon. He was treated preoperatively with a continuous intravenous infusion of 5 per cent glucose in saline and an indwelling Levine tube. Four days later, under general anesthesia, a partial colectomy with removal of a malignant tumor was performed and a temporary colostomy was established. The continuous intravenous infusion was maintained for five days postoperatively. Not until one week after operation was the patient started on a low residue diet.

The nurses' records at this time, one week after operation, made note of the patient's complaint of a sore, burning mouth. In spite of frequently repeated, painstaking oral hygiene, he still complained of the pain in the mouth. This rapidly became worse to the point that any attempt at eating or drinking resulted in such marked exacerbation of the discomfort that the patient literally went on a hunger strike. His mental state changed so that he was uncoöperative, disoriented and confused. The dental department saw him at this time and noted: "poor oral hygiene; distributed over the mucosa of the lips, cheeks, vestibule, hard palate, fauces and gingiva are flat, light tan-colored serpiginous patches with a red border." He was treated locally with gentian violet, but the lesions still progressed. Two days later, when seen by us, there were in addition, ulcers and bullae on the oral mucous membrane. The tongue was moderately smooth, but not fiery red. The gums were heaped up, edematous and reddish-purple in color. He complained bitterly of burning of the mouth and refused water almost as one with hydrophobia.

Because of the relatively slight involvement of the tongue, he was started on riboflavin concentrate, equivalent to 10 mg., three times a day. After 24 hours there was still extension of the lesion. Therefore, he was further treated with 300 mg. of nicotinic acid intravenously, administered in three divided doses each day. There immediately ensued a most dramatic change. Overnight there was a marked decrease in his symptoms and he began to eat. His mental state cleared rapidly. Objectively, within 24 hours, the angry, gray slough overlying the ulcers cleared considerably. Within five days the lesions had entirely disappeared. His appetite improved considerably. Within two weeks, he had recuperated sufficiently to permit the surgeons to proceed with closure of the colostomy. During the second operative period vitamin therapy was maintained. There was no recurrence of the lesion.

The history, the preliminary chain of events, the nature of the lesions, the mental symptoms, and the clear-cut rapid complete response to the administration of specific vitamin therapy support the diagnosis of a vitamin B complex deficiency, predominantly of niacin.

EDITORIAL

HYPERGLYCEMIA AND GLYCOSURIA AS MEANS OF CONTROLLING PROTAMINE ZINC INSULIN ADMINISTRATION IN DIABETES

BEFORE insulin was discovered dietary restriction and control constituted the only therapeutic procedures which materially affected the course of diabetes. As a guide to the effectiveness of treatment, hyperglycemia and the attendant glycosuria were universally employed. Control of the glycosuria was followed by improvement, whereas failure to accomplish this meant active and progressive disease. Naunyn (1906) was among the first to formulate this observation precisely. "In many cases of diabetes glycosuria shows a decided tendency to progress. . . . But in the majority of cases the progressiveness of the glycosuria is only the expression of the bad influence which the glycosuria itself exerts on the tolerance . . . the glycosuria should be abolished on account of the favorable influence which the aglycosuric condition has on tolerance." It is not sufficient "to maintain the patient for a long time in an endurable condition of life . . . treatment includes a broader, more definite purpose, namely to strengthen (to improve) a disturbed function or at least to stop its further deterioration (the progressive development of the disease)." [1] Many confirmatory observations have been made in experimentally produced diabetes in animals. It was but natural to conclude that, since hyperglycemia and glycosuria are signs of ill omen, they are presumably in themselves directly injurious.

The introduction of soluble insulin increased enormously the effectiveness of treatment. For the more severe types of the disease, however, it can not be said to have simplified treatment as much as might be desired. Abolition of glycosuria and control of hyperglycemia have been the criteria of successful management, and in order to accomplish this it is often necessary to distribute the food with painstaking care and administer three or four doses of insulin a day.

The introduction of the relatively insoluble and slowly absorbed protamine zinc insulin promised to simplify procedures greatly. As the effect of a single dose, if not too small, is maintained in some degree for 24 hours or more, it became possible, theoretically at least, to administer the entire daily requirement in a single early morning dose. Although this has proved highly satisfactory in the mild cases, in the more severe cases it is often difficult or impossible to abolish glycosuria without incurring severe insulin reactions. This has been combated by redistribution of the diet, but often an extra morning dose of soluble insulin, or even two or three such doses are required if the usual criteria for adequate control are to be fully met. Such

[1] As translated by JOSLIN, E. P.: The campaign against diabetes (correspondence), Jr. Am. Med. Assoc., 1942, cxx, 860.

difficulties have led some clinicians to feel that adequate control of severe cases with protamine insulin alone is impracticable if not impossible.

As insulin reactions are much more disturbing and probably more dangerous than a moderate glycosuria, inevitably some patients were maintained on a régime which resulted in the excretion of substantial amounts of glucose. This was found not to be followed by any immediate obvious injury. Even as meticulous and conservative a clinician as Joslin [2] regarded control as adequate if the patient was otherwise in satisfactory condition and if the glucose excreted did not exceed 10 per cent of the carbohydrate intake. Others have been much more daring. Thus Tolstoi and Weber [3] reported careful metabolic studies on two patients with severe diabetes who were maintained on an adequate diet and given one daily dose of protamine zinc insulin which just failed to cause hypoglycemic reactions. These patients felt well, were in nitrogen equilibrium and showed only trivial fluctuations in weight in spite of constant heavy glycosuria. These observers [4] later reported a study of 84 cases followed for one year in the out patient department and treated in a similar manner with no special effort to keep the urine free from sugar. Of these, 27 patients excreted glucose persistently and in large amounts. Nevertheless they continued at work, with four exceptions maintained or increased their weight, were free from symptoms and were believed to be as free from infections as the group whose urine was substantially sugar free. The authors concluded that glucose must have been utilized in quantities adequate for their needs, and that the important factor in treatment "is not how much sugar is excreted, but how much is utilized." They therefore suggested as criteria of satisfactory treatment, maintenance of weight, absence of ketosis, freedom from the usual symptoms of diabetes and avoidance of hypoglycemic reactions. Under such circumstances they believe glycosuria and hyperglycemia are immaterial and may be even advantageous in as far as the latter protects from hypoglycemic insulin reactions.

Partly in answer to criticisms of this procedure by Joslin [5] and others, in a recent number of the ANNALS OF INTERNAL MEDICINE Tolstoi, Almy and Toscani [6] again have reported a metabolic study of a man with severe diabetes treated successfully by this method, according to their standards. Although the patient constantly excreted large amounts of glucose over the six weeks' period, he was in positive nitrogen balance, maintained weight

[2] JOSLIN, E. P.: Diabetes and protamine insulin, Mil. Surg., 1938, lxxxii, 1.

[3] TOLSTOI, E., and WEBER, F. C., JR.: Protamine zinc insulin: a metabolic study. Treatment in two severe cases of diabetes with equally and unequally divided diets, with comments on criteria for treatment, Arch. Int. Med., 1939, lxiv, 91–104.

[4] TOLSTOI, E., and WEBER, F. C., JR.: Protamine zinc insulin: a clinical study. Report of a group of diabetic patients in whose cases glycosuria was disregarded for one year, Arch. Int. Med., 1940, lxvi, 675–678.

[5] JOSLIN, E. P.: Treatment of diabetes (correspondence), Jr. Am. Med. Assoc., 1940, cxv, 1038–1039.

[6] TOLSTOI, E., ALMY, T. P., and TOSCANI, V.: Treatment of diabetes mellitus with protamine insulin: is a persistent glycosuria harmful? A metabolic study of a severe case, ANN. INT. MED., 1942, xvi, 893–903.

and was free from symptoms. Previous attempts to control the glycosuria by multiple doses of soluble insulin had not given as satisfactory clinical results. In spite of marked glycosuria over a period of three years, this patient is reported to have shown no special susceptibility to infection, no impairment of renal function and no demonstrable increase in atherosclerosis. They reaffirm their belief that glycosuria is harmless if adequate utilization of carbohydrate is secured (by the use of protamine zinc insulin).

These views have been severely criticized, largely on the ground that hyperglycemia is directly harmful in itself. It has been regarded as a direct stimulus to insulin secretion, and overstimulation of a diseased organ may be expected to damage it still further. Hyperglycemia is also generally blamed for the susceptibility to infection and the tendency to atherosclerotic changes so characteristic of uncontrolled diabetes, although there is no real proof that they are simply a direct result of hyperglycemia.

The formerly held concept that the primary fault in diabetes is loss of the ability to utilize carbohydrate and that insulin acts simply by bringing about better utilization is not an adequate explanation of the metabolic disturbances in this disease. Perhaps equally important are the inability to store carbohydrate as glycogen, and the tendency to excessive gluconeogenesis from protein. These disturbances are also controlled by insulin. Furthermore the completely diabetic animal retains the capacity to utilize significant amounts of carbohydrate, provided there is an extreme degree of hyperglycemia or great undernutrition. Neither is the height of the blood sugar a reliable indication of the degree to which glucose is utilized. Thus Bridge and Winter [7] have shown that in patients under treatment, fluctuations in the blood sugar from 100 to 300 mg. per cent in the course of the day are not accompanied by corresponding or significant changes in the respiratory quotient. It seems clear that hyperglycemia can not be accepted as the sole criterion of adequate control and is probably not the most important single criterion.

Although it is difficult to determine directly the harm caused by hyperglycemia itself in human diabetes, there is highly suggestive evidence in animal experiments that hyperglycemia is harmful in itself. In the dog and in the partially depancreatized cat, as shown for example by Lukens and Dohan,[8] repeated injections of anterior pituitary extract can produce a permanent and progressive diabetes associated with histological changes in the islands of Langerhans. If, however, insulin was administered, or if the cats were fasting or if they were on a high fat, low protein diet, permanent diabetes would not develop. Furthermore, if treatment of the established diabetes was started early before irreversible changes in the islands had occurred, either by the administration of insulin or by a reduction of the meat in the diet, the disease could be arrested and the islands recover normal struc-

[7] Bridge, E. M., and Winter, E. A.: Diabetes, insulin action and the respiratory quotient, Bull. Johns Hopkins Hosp., 1939, lxiv, 257.

[8] Lukens, F. D. W., and Dohan, F. C.: Pituitary diabetes in the cat; recovery following insulin or dietary treatment, Endocrinology, 1942, xxx, 175–202.

ture, and a full diet could be resumed later without recurrence of the diabetes. In general, diabetes with injury to the islands developed only under conditions which caused a persistent hyperglycemia, and it was arrested by procedures which abolished hyperglycemia. It was even possible to cure the diabetes by lowering the blood sugar with phlorhizin, which as far as is known lowers blood sugar solely by increasing glycosuria. Although alternative explanations of the effect of diet on this experimental diabetes can be offered, the weight of evidence against hyperglycemia seems strong. These observations indicating the direct harmfulness of hyperglycemia in animals, however, can not be applied to man without further study.

As far as the general management of human diabetes is concerned, in the light of present knowledge it would not seem prudent to disregard hyperglycemia and glycosuria. This would encourage carelessness in treatment and possibly lead to the injury of many patients. In patients who are receiving protamine zinc insulin, a moderate degree of glycosuria appears to be harmless. For the present, however, a real effort should be made to avoid persistent and marked glycosuria. How marked a degree of glycosuria can safely be disregarded and how far the effort to control it should be carried are the questions at issue, and at present no final answer to them can be given. It would seem that the effort should at least include careful control and, if necessary, redistribution of the diet and one supplementary morning dose of soluble insulin. In the relatively small group of patients of whom control is difficult, it may well be better to disregard glycosuria, if conditions are otherwise satisfactory, rather than risk hypoglycemic reactions or insist upon a complicated and burdensome régime which interferes with their normal activities. Tolstoi has shown that patients can be so maintained in a state of comfort and efficiency and with no injury obvious, at least during a three or four years' observation period. Until it has been demonstrated that hyperglycemia can be endured without injury over a much longer period, however, it would be unwise to encourage disregarding it in the routine treatment of diabetes.

REVIEWS

Introduction to Physical Biochemistry. By J. M. JOHLIN, Ph.D., D.Sc. 231 pages; 24 × 16.5 cm. Paul B. Hoeber, Inc., New York. 1941. Price, $2.75.

According to the author much of the material in the book under review has been presented to his students of biochemistry, as a preliminary survey of some of the fundamental facts which they must know for a better understanding of various biological phenomena and of laboratory procedures. The introduction includes a short chapter on the functions and composition of blood. Then follow concise but adequate chapters on the physical and chemical properties of water, hemoglobin, the gas laws, the colligative properties of solutions, the characteristics of the colloidal state of matter, chemical equilibrium and the law of mass action, buffer systems, the properties of indicators, oxidation-reduction potentials, the respiratory functions of blood, the acid-base balance of the blood, and, finally, a chapter on oxidation-reduction systems. In addition a chapter on logarithms has been added. This book should prove valuable to the student or clinician who desires an increased knowledge of these subjects.

E. G. S.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Cancer of the Uterus. By ELIZABETH HURDON, C.B.E., M.D. 188 pages; 22 × 14.5 cm. 1942. Oxford University Press, New York. Price, $5.00.

Practical Survey of Chemistry and Metabolism of the Skin. By MORRIS MARKOWITZ, M.D. 196 pages; 20.5 × 13.5 cm. 1942. The Blakiston Company, Philadelphia. Price, $3.50.

Fundamentals of Psychiatry. By EDWARD A. STRECKER, M.D., Sc.D., F.A.C.P. 201 pages; 19.5 × 13 cm. 1942. J. B. Lippincott Company, Philadelphia. Price, $3.00.

Love Against Hate. By KARL MENNINGER, M.D. 311 pages; 22 × 15 cm. 1942. Harcourt, Brace and Company, New York. Price, $3.50.

Biological Symposia, Vol. IX. Sex Hormones. Edited by F. C. KOCH AND PHILIP E. SMITH. 146 pages; 25 × 17.5 cm. 1942. The Jaques Cattell Press, Lancaster, Pennsylvania. Price, $2.50.

Public Health and Preventive Medicine. 2 volumes. By MORTON C. KAHN, M.A., Ph.D., D.Sc. 534 pages; 22 × 14 cm. (each volume). 1942. Oxford University Press, New York. Price, $4.00 the set.

Diseases of the Gastro-Intestinal Tract. By ASHER WINKELSTEIN, M.D., B.S. 195 pages; 22 × 14 cm. 1942. Oxford University Press, New York. Price, $2.00.

Urology. By WILLIAM H. MENCHER, A.B., M.D., F.A.C.S. 204 pages; 22 × 14 cm. 1942. Oxford University Press, New York. Price, $2.00.

Gynecologic Surgery. By MORRIS A. GOLDBERGER, M.D., F.A.C.S. 164 pages; 22 × 14 cm. 1942. Oxford University Press, New York. Price, $2.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

In previous issues of this journal, the names of 1,065 members of the College serving in the armed forces of their country were recorded. Herewith are reported the names of 57 additional members bringing the grand total to 1,122.

F. Dennette Adams
Ruel L. Alden
Samuel S. Altshuler
Benjamin M. Baker, Jr.
Raymond L. Barrett
Carl B. Beeman
James B. Berardi
Gerald Blankfort
Charles M. Caravati
Julius Chasnoff
John B. D'Albora
George P. Denny
Richard D. Evans
Milton B. Filberbaum
Ralph L. Fitts
Paul D. Foster
Aime N. Fregeau
Franklin W. Fry
Irving Greenfield
T. Haynes Harvill
Kendall B. Holmes
John A. Hookey, Sr.
Sidney W. Jennes
James P. Jordan
Roger H. Keane
Bruce D. Kenamore
*Edwin P. Kolb
Samuel I. Kooperstein
Louis A. M. Krause
William A. Lange
Clarence W. LeDoux
John E. Manley
John B. McKee
James H. McNeill
Edgar M. McPeak
Ferrall H. Moore
Harold W. Palmer
Martin Patmos
Richard O. Pfaff
Russell C. Pigford
Milton M. Portis
H. William Primakoff
Clark P. Pritchett
Norman Reider
Howard A. Rusk
John B. Schwedel
John W. Shadle
Emil M. Shebesta
Ralph E. Swope
Milo K. Tedstrom
Martin V. B. Teem
Edward G. Thorp
T. Lloyd Tyson
Lee D. van Antwerp
Norton W. Voorhies
Joseph O. Weilbaecher, Jr.
Udo J. Wile

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows:

American Board of Internal Medicine:
William A. Werrell, M.D., Assistant Secretary
1301 University Ave.
Madison, Wis.

Written Examinations: Will be given in various cities and at a number of Army and Naval stations, February 15, 1943.

Oral Examinations: Dates and place will be announced later.

American Board of Dermatology and Syphilology:
C. Guy Lane, M.D., Secretary
416 Marlboro St.
Boston, Mass.

Written Examinations: Will be given in various centers during October, 1943.

Oral Examinations: Philadelphia, Pa., December 3–4, 1943.

* Retired to inactive duty.

AMERICAN BOARD OF PATHOLOGY:
F. W. Hartman, M.D., Secretary
Henry Ford Hospital
Detroit, Mich.

Written and Oral Examinations: Spring, 1943; probably in connection with the meeting of the American Association of Pathologists and Bacteriologists, Chicago, Ill., April 1–2, 1943.

AMERICAN BOARD OF PEDIATRICS:
C. A. Aldrich, M.D., Secretary
707 Fullerton Ave.
Chicago, Ill.

Written Examinations: Will be given in various centers, February 12, 1943.

Oral Examinations: St. Louis, Mo., March 27–28, 1943 (closed); New York, N. Y., April 24–25, 1943 (closed).

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY:
Walter Freeman, M.D., Secretary
1028 Connecticut Ave., N. W.
Washington, D. C.

Oral Examinations: Detroit, Mich., April, 1943, in advance of the meeting of the American Psychiatric Association. Applications must be filed before March 1, 1943.

AMERICAN BOARD OF RADIOLOGY:
B. R. Kirklin, M.D., Secretary
Mayo Clinic
Rochester, Minn.

Oral Examinations: Spring and Fall, 1943; dates and place yet to be announced.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

James E. Ash, F.A.C.P., Colonel, (MC), U. S. Army—"Atlas of Dental and Oral Pathology," "Atlas of Ophthalmic Pathology" and "Atlas of Otolaryngic Pathology";

Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y.—"Therapeutics of Infancy and Childhood," Vols. II and III;

Dr. Malcolm T. MacEachern, F. A. C. P., Chicago, Ill.—"Hospital Organization and Management" and "Manual on Obstetric Practice in Hospitals";

Dr. Francis M. Pottenger, Jr., F.A.C.P., Monrovia, Calif.—"History of Randleigh Farm."

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), U. S. Army—1 reprint;
Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.,—2 reprints;
Dr. Verne S. Caviness, F.A.C.P., Raleigh, N. C.—2 reprints;
Dr. Nathan W. Chaikin (Associate), New York, N. Y.—1 reprint;
Dr. William Dameshek, F.A.C.P., Boston, Mass.—1 reprint;
Dr. James M. Flynn, F.A.C.P., Rochester, N. Y.—1 reprint;
Dr. Hugh Jeter, F.A.C.P., Oklahoma City, Okla.—1 reprint;
Dr. Richard D. Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
Dr. Harry D. Leinoff (Associate), New York, N. Y.—2 reprints;
Dr. William H. Marshall, F.A.C.P., Flint, Mich.—1 reprint;
Horace P. Marvin, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—1 reprint;
Robert B. Radl, F.A.C.P., Major, (MC), U. S. Army—1 reprint;
Dr. Harry B. Thomas, F.A.C.P., York, Pa.—1 reprint;
Dr. Howard Wakefield, F.A.C.P., Chicago, Ill.—1 reprint;
Leon H. Warren (Associate), Major, (MC), U. S. Army—3 reprints;

Dr. William A. Winn (Associate), Springville, Calif.—2 reprints;
Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa.—1 reprint.

Sanford W. French, F.A.C.P., Colonel, (MC), U. S. Army, has donated a publication entitled "Report on Allergy Clinics in Fourth Service Command, from April 1 to October 1, 1942" to the College Library. This report was prepared under the direction of Colonel French.

Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., has donated a bound volume of reprints entitled "The Publications of George R. Herrmann, M.D., and Associates, 1928–1938," to our Library.

PRESENT A. C. P. OFFICERS, REGENTS AND GOVERNORS WILL SERVE DURING WAR

Inasmuch as the By-laws of the American College of Physicians provide that all Officers, Regents and Governors (except in the case of vacancies due to death or resignation) shall be elected by the Fellows and Masters of the College at an Annual Business Meeting, and since the Annual Sessions have been cancelled for the duration of the war and it becomes, therefore, impractical and next to impossible to hold an Annual Business Meeting of the members, it is apparent that the present Officers, Regents and Governors must continue to serve until the provisions of the By-laws may be fulfilled.

Announcement was received on December 11, 1942, that Dr. Hugh J. Morgan, F.A.C.P., Regent of the College, had been promoted from Colonel to Brigadier General in the Medical Corps of the U. S. Army, and is attached to the Office of the Surgeon General in Washington, D. C.

Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif., has been elected President of the Alameda County Medical Association.

Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa., has resigned from the U. S. Public Health Service and has assumed the duties of Pathologist at St. Luke's Hospital, Bethlehem.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., spoke on "Medical Aspects of Nutrition" at a meeting of the Berks County (Pa.) Medical Society, Reading, November 10, 1942.

Dr. Paul F. Whitaker, F.A.C.P., Kinston, N. C., has resumed a limited consulting practice in Kinston with offices in the Memorial General Hospital.

At a recent meeting of the Mississippi Valley Medical Editors' Association, Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was reëlected Secretary and Dr. George B. Lake (Associate), Waukegan, Ill., was named a member of the Executive Committee.

The 10th Annual Assembly of the Omaha Mid-West Clinical Society was held in Omaha, Nebr., on October 26–30, 1942. This meeting consisted of general assemblies, clinics, lectures and scientific and technical exhibits. Among the distinguished guests at this meeting were:

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—"Leukemia," "Undulant Fever";
Dr. Herman H. Riecker, F.A.C.P., Ann Arbor, Mich.—"The Clinical Anticipation of Disease," "Essential Hypertension";
Dr. Francis E. Senear, F.A.C.P., Chicago, Ill.—"Fungous Infections of the Skin," "New Drugs Used in Dermatology";
Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—"Diagnostic and Therapeutic Problems of the Menopause," "Use of Pituitary and Ovarian Therapy, Disturbances of Menstrual Rhythm and Fertility";
Dr. Irvine H. Page (Associate), Indianapolis, Ind.—"Background for Modern Concepts of the Experimental Treatment of Hypertension," "Medical and Surgical Management of Hypertension."

Among the local Fellows of the College who participated in the program were:

Dr. Lynn T. Hall, F.A.C.P.—"The Present Status of Liver Tests";
Dr. Maurice C. Howard, F.A.C.P.—"Management of Gastric Hemorrhage";
Dr. Ernest Kelley, F.A.C.P.—"Electric Shock in the Treatment of Psychoses";
Dr. Ernest L. MacQuiddy, F.A.C.P.—"Oral Therapy in Hay Fever: A Review of Results in 1941 and 1942";
Dr. Frederick W. Niehaus, F.A.C.P.—"Chest Pains Simulating an Anginal Syndrome";
Dr. Abraham S. Rubnitz, F.A.C.P.—"Myocardial Changes Following Coronary Thrombosis";
Dr. Adolph Sachs, F.A.C.P.—"Renal Hypertension";
Dr. Warren Thompson, F.A.C.P.—"Hypothyroidism";
Dr. Edmond M. Walsh, F.A.C.P.—"Management of Difficult Diabetics";
Dr. Harrison A. Wigton, F.A.C.P.—"Intracranial Hemorrhage."

Among the Omaha members of the College who presented scientific exhibits were:

Dr. M. William Barry, F.A.C.P., and Dr. Ben Slutzky (Associate)—"Carotid Sinus Syndrome";
Dr. F. Lowell Dunn, F.A.C.P.—"Cathode Ray Visualization of Lung and Heart Sounds";
Dr. Adolph Sachs, F.A.C.P., and Dr. Ben Slutzky (Associate)—"The Electrocardiophonograph—Heart Sounds";
Dr. Albert F. Tyler, F.A.C.P.—"Radiation Therapy of the Breast," "Diseases of the Lungs and Mediastinum in Childhood."

Dr. Russell L. Haden conducted a clinic on "Menopausal Arthralgia; Infectious Arthritis; Gout Complicated by Hypertrophic Arthritis," Dr. Francis E. Senear, a clinic on "Dermatology," and Dr. Elmer L. Sevringhaus, a clinic on "Postpartum Obesity with Menorrhagia and Sterility; Excessive Obesity with Metrorrhagia; Obesity with Hypomenorrhea and Premenstrual Tension."

Dr. W. Warner Watkins, F.A.C.P., Phoenix, Ariz., has resigned as Secretary of the Arizona State Medical Association and Dr. Frank J. Milloy, F.A.C.P., Phoenix, has been named as his successor.

On November 23, 1942, Dr. Italo F. Volini, F.A.C.P., Chicago, Ill., addressed the Chicago Society of Internal Medicine. Dr. Volini spoke on "Studies on Mercurial Diuresis: Sudden Death Following Intravenous Injection; Report of Three Cases with Electrocardiographic Studies."

On the occasion of his seventieth birthday, Dr. Emanuel Libman, F.A.C.P., New York, N. Y., was honored at a dinner at the Waldorf-Astoria, October 31, 1942. The dinner honoring Dr. Libman was sponsored by the American Friends of the Hebrew University and the American Jewish Physicians Committee. The speakers included Dr. Joseph H. Pratt, F.A.C.P., Boston, Mass., and Leonard G. Rowntree, F.A.C.P., Colonel, (MC), U. S. Army.

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., Dr. Udo J. Wile, F.A.C.P., U. S. Public Health Service, and Dr. Reginald Fitz, F.A.C.P., Boston, Mass., were among those who conducted a postgraduate refresher course sponsored by the Alumni Association of the Medical College of the State of South Carolina in Charleston, November 4–5, 1942.

Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio, spoke on "Aortic Stenosis" at the Founders' Day Banquet of the Association.

Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., will conduct a course in "Electrocardiographic Interpretation" at the Michael Reese Hospital, Chicago, beginning February 17, 1943. The class will meet once each week for a period of twelve weeks.

Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y., David Ulmar, F.A.C.P., Lieutenant Commander, (MC), U. S. Navy, and Dr. Edgar Mayer, F.A.C.P., New York, N. Y., were among those who conducted a clinical session on "Chronic Pulmonary Diseases" sponsored by the Tuberculosis Sanatorium Conference of Metropolitan New York, December 9, 1942.

Dr. Irvine H. Page (Associate), Indianapolis, Ind., gave the Walter L. Niles Memorial Lecture sponsored by Nu Sigma Nu at Cornell University Medical College, October 20, 1942. Dr. Page spoke on "The Modern Concept of Hypertension."

Dr. Oswald F. Hedley, F.A.C.P., U. S. Public Health Service, Bethesda, Md., discussed "The Cardiac in Industry" at a meeting of the New York Heart Association, December 1, 1942.

Ursinus College, Collegeville, Pa., has named its new science building the "Pfahler Hall of Science" in honor of Dr. George E. Pfahler, F.A.C.P., Philadelphia, Pa. Dr. Pfahler has been a member of the Board of Directors of Ursinus College since 1935 and has been Professor of Radiology at the University of Pennsylvania School of Medicine, Philadelphia, since 1916.

On October 30, 1942, Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., spoke on "The Value of the Roentgen Rays to Diagnosis as It Pertains to the Physician Doing General Work" at a medical conference sponsored by the Medical Replacement Training Center at Camp Barkeley, Tex.

Dr. Frederic M. Hanes, F.A.C.P., Florence McAlister Professor of Medicine at Duke University College of Medicine, Durham, N. C., was recently appointed Director of the Durham Emergency Base Hospital Unit, which has been established for the protection of the civilian population during the war.

The Fifth District Medical Society of Georgia held a semiannual meeting in Atlanta, October 19, 1942. Among the speakers were:

Donald T. Chamberlin (Associate), Major, (MC), U. S. Army,—"Functional Digestive Diseases as Encountered at the Lawson General Hospital";
Walter M. Bartlett, F.A.C.P., Major, (MC), U. S. Army,—"Three Thousand Hours of Cardiovascular Diseases in a General Hospital."

Dr. Lawrence Reynolds, F.A.C.P., Detroit, Mich., delivered the second Henry K. Pancoast Memorial Lecture before the Philadelphia Roentgen Ray Society and the Philadelphia College of Physicians on November 5, 1942. Dr. Reynolds spoke on "Newer Investigations of Radiation Effects and Their Clinical Application."

At the recent fall meeting of the Society for the Study of Asthma and Allied Conditions in New York, N. Y., Dr. John A. Kolmer, F.A.C.P., Philadelphia, Pa., spoke on "Biotherapy and Chemotherapy of the Respiratory Tract Diseases," Dr. Milton B Cohen, F.A.C.P., Cleveland, Ohio, on "Preliminary Report on the Fractionation of Ragweed Pollen and Immunological Studies with These Fractions," and Dr. Abner M. Fuchs (Associate), New York, N. Y., on "The Treatment of Hay Fever with Gelatin Pollen Extracts."

At the annual session of the Association of American Medical Colleges held in Louisville, Ky., October 28, 1942, Dr. Waller S. Leathers, F.A.C.P., Nashville, Tenn., was installed as President and Dr. John Walker Moore, F.A.C.P., Louisville, was chosen Vice President.

The 28th Annual Meeting of the Radiological Society of North America was held in Chicago, Ill., November 30–December 4, 1942. Among the speakers were:

Dr. Benjamin H. Orndoff, F.A.C.P., Chicago, "Roentgen Castration for Malignant and Nonmalignant Diseases";
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—"Plastic Induration of the Penis."

The Royal College of Physicians in Edinburgh has awarded its Cullen Prize to Dr. Thomas Addis, F.A.C.P., Professor of Medicine at Stanford University School of Medicine, San Francisco, Calif., for "the greatest benefit done to practical medicine in the last four years." The research work of Dr. Addis included extensive study on the kidney.

Dr. Andrew C. Ivy, F.A.C.P., who was recently appointed Chief Scientific Director of the new U. S. Naval Medical Research Institute in Bethesda, Md., delivered the fourteenth annual William T. Belfield Memorial Lecture at a meeting of the Chicago Urological Society, November 19, 1942. The subject of Dr. Ivy's lecture was "The Physiology of the Urinary Bladder, with Special Reference to Its Nerve Supply."

At the twenty-seventh Annual Dinner of the Institute of Medicine of Chicago, December 2, 1942, Dr. James B. Herrick, M.A.C.P., was honored for his many years of service to the Institute. Dr. Herrick was one of the founders of the Institute of Medicine. During 1925 he served as President of the Institute and he has been an active member of the Board of Governors since 1915.

The New York Academy of Medicine and the New York Heart Association are coöperating in a series of lectures on "Cardiovascular Diseases." Among those who will participate in these lectures are:

January 27, 1943—Dr. Edwin P. Maynard, Jr., F.A.C.P., Brooklyn, N. Y.—"The Management of Cardiovascular Syphilis";
March 24, 1943—Irving S. Wright, F.A.C.P., Lieutenant Colonel, (MC), U. S. Army—"The Management of Peripheral Vascular Disease";
April 28, 1943—Dr. Currier McEwen, F.A.C.P., New York, N. Y.—"The Management of Rheumatic Fever";
May 26, 1943—Dr. Arthur C. De Graff, F.A.C.P., New York, N. Y.—"The Management of Cardiac Arrhythmias."

Dr. Israel Davidsohn, F.A.C.P., Chicago, Ill., has been named Editor-in-Chief of the American Journal of Clinical Pathology.

Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, Md., has been elected President of the Southern Tuberculosis Conference.

At the annual meeting of the Central Society for Clinical Research held in Chicago, Ill., November 6–7, 1942, Dr. John Walker Moore, F.A.C.P., Louisville, Ky., was elected President. Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., was named Vice President and Dr. Carl V. Moore, F.A.C.P., St. Louis, Mo., Secretary-Treasurer.

The Dallas Southern Clinical Society has cancelled its 1943 Spring Clinical Conference because of the national emergency.

Dr. Robert U. Patterson, F.A.C.P., at one time Surgeon General of the U. S. Army, and for the last several years Dean of the University of Oklahoma School of Medicine, has recently accepted the Deanship of the University of Maryland School of Medicine, Baltimore.

Dr. Edwin G. Bannick Appointed Acting Governor for Washington

The Executive Committee of the Board of Regents of the College recently appointed Dr. Edwin G. Bannick, F.A.C.P., Medical and Dental Bldg., Seattle, Wash., Acting Governor for the State of Washington, during the absence of Dr. Charles E. Watts, who is serving as Commander in the Medical Corps of the U. S. Navy on duty in the Pacific.

Regional Meeting and "Postgraduate Nights" Held in Chicago Area

The American College of Physicians conducted "Postgraduate Nights" programs, November 19–20, and held a Regional Meeting, including the States of Illinois, Indiana, Iowa, Michigan and Wisconsin, at the Drake Hotel, Chicago, on November 21. At the "Postgraduate Nights" meeting at Camp Grant, Ill., there were in attendance somewhat over two hundred Medical Officers of the Army, with a few Medical Officers in attendance from the Navy. At the program at the Great Lakes Naval Hospital approximately two hundred Medical Officers of the Navy and a few Medical Officers from the Army were in attendance. Both programs were received with enthusiasm and appreciation.

The Regional Meeting in Chicago was the first real attempt to combine several States. Twenty-five per cent (25%) of the Fellows and Associates of the College located in the States represented were in attendance. An analysis of attendance is as follows:

	Master	Fellows	Associates	Guests	Total	Civilian Doctors	Service Doctors
Illinois	1	60	24	89	174	130	44
Indiana		10	2	2	14	12	2
Iowa		8	1		9	9	
Michigan		19	12	6	37	25	12
Wisconsin		10	5	4	19	12	7
Miscellaneous:							
District of Columbia		1		1	2		2
Georgia		1			1	1	
Kentucky				1	1		1
Maryland		1			1		1
Massachusetts		1			1	1	
Minnesota		1			1	1	
Missouri				1	1		1
Oklahoma		1			1	1	
Pennsylvania				1	1	1	
Ontario, Canada				1	1		1
	1	113	44	106	264*	193	71

* If we add to this total at the Regional Meeting approximately four hundred additional service physicians who attended the "Postgraduate Nights" program, it makes a grand total of 664.

The programs were as follows:

Postgraduate Nights

Thursday, November 19, 1942

OFFICERS CLUB

CAMP GRANT, ILLINOIS

8:00 P.M.

Presiding Officer

JOHN M. WILLIS, M.D., F.A.C.P.
Brigadier General, M.C., U. S. Army
Commanding General, Camp Grant

1. "Shock." Warren H. Cole, M.D., F.A.C.S. (by invitation), Professor of Surgery and Head of the Department of Surgery, University of Illinois College of Medicine, Chicago, Ill.
2. "Pre-operative Preparation of Patients." Robert W. Keeton, M.D., F.A.C.P., Professor of Medicine and Head of the Department of Internal Medicine, University of Illinois College of Medicine, Chicago, Ill.
3. "Penetrating Injuries of the Chest." Willard Van Hazel, M.D., F.A.C.S. (by invitation), Professor of Surgery, University of Illinois College of Medicine, Chicago, Ill.
4. "Atypical (Virus ?) Pneumonia." Clayton Loosli, M.D. (by invitation), Assistant Professor of Medicine, University of Chicago, Chicago, Ill.

Friday, November 20, 1942

GREAT LAKES NAVAL HOSPITAL

GREAT LAKES, ILLINOIS

8:00 P.M.

Presiding Officer

WILLIAM E. EATON, M.D., F.A.C.S.
Captain, M.C., U. S. Navy
Commanding Officer, Great Lakes Naval Hospital

1. "35 mm. Photofluorography as Used in the Navy." Robert E. Duncan, M.D., F.A.C.P. (by appointment), Captain, M.C., U. S. Navy; Executive Officer, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Md.
2. "Syphilitic Heart Disease." James E. Paullin, M.D., F.A.C.P., President, American College of Physicians; President-Elect, American Medical Association; Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Ga.
3. "Clinical Signs of Nerve Regeneration." Lewis J. Pollock, M.D. (by invitation), Professor and Head of the Department of Nervous and Mental Diseases, Northwestern University Medical School, Chicago, Ill.
4. "Recent Advances in the Treatment of Infectious Diseases." Archibald L. Hoyne, M.D., F.A.C.P., Professor of Pediatrics, University of Chicago; Director and Chief of the Department of Contagious Diseases, Cook County Hospital and the Municipal Contagious Hospital, Chicago, Ill.

Regional Meeting

LEROY H. SLOAN, M.D., F.A.C.P.
Governor for Northern Illinois

WILLARD O. THOMPSON, M.D., F.A.C.P.
Chairman, Program and Arrangements Committee

Chicago

Saturday, November 21, 1942

MORNING SESSION—9:00 A.M.

"The Treatment of Arterial Hypertension with Ascorbic Acid." Nathan S. Davis, III, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill.

"Nutritional Problems in War Time." Clifford J. Barborka, M.D., F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill.

"The Effect of Altitude on Peripheral Circulation." Carl Johnson, M.D. (by invitation), A. Wilson Smith, M.D. (by invitation) and Thomas J. Coogan, M.D., F.A.C.P., St. Luke's Hospital, Chicago, Ill.

"Significance of Joint Pains Caused by Sterile Streptococcus Toxin." Paul S. Rhoads, M.D., F.A.C.P., Associate Professor of Medicine, and Melvin E. Afremow, M.D. (by invitation), Northwestern University Medical School and Cook County Hospital, Chicago, Ill.

"Maintaining High Standards of Medical Practice with Decreasing Personnel." Roscoe L. Sensenich, M.D., F.A.C.P., Board of Trustees, American Medical Association, South Bend, Ind.

"Acute Nephritis and the Effect of Sulphonamides on the Kidney." Francis D. Murphy, M.D., F.A.C.P., Professor of Medicine and Head of the Department, Marquette University School of Medicine, Milwaukee, Wis.

"Persistence of Estrogen Induced Sexual Development." Henry H. Turner, M.D., F.A.C.P., Associate Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

"Army Casualties—Honolulu, December 7, 1941." T. Donald McCarthy, M.D. (by invitation), Major, Medical Corps, U. S. Army, Camp Grant, Ill.

Intermission

"Psychoneuroses in War Time." Lloyd H. Ziegler, M.D. (by invitation), Professor of Psychiatry, University of Illinois College of Medicine; Director, Milwaukee Sanitarium, Wauwatosa, Wis.

"Bronchoscopic Observations in Atypical Pneumonia." Paul H. Holinger, M.D., F.A.C.S. (by invitation), Director, Department of Peroral Endoscopy, St. Luke's Hospital, and University of Illinois College of Medicine, Chicago, Ill.

"Recent Advances in the Treatment of Contagious Diseases." Archibald L. Hoyne, M.D., F.A.C.P., Chief, Contagious Disease Department, Cook County Hospital and Municipal Contagious Hospital, Chicago, Ill.

"Physical Therapy in Civilian Defense." John S. Coulter, M.D., F.A.C.S. (by invitation), Regional Medical Officer, 6th Civilian Defense Region, Chicago, Ill.

"Gastro-intestinal Disorders in the Armed Forces." Ralph C. Brown, M.D. (by invitation), Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

"Aspiration Pneumonia." Carl W. Apfelbach, M.D. (by invitation), Professor of Pathology, and Ernest E. Irons, M.D., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill.

AFTERNOON SESSION—2:00 P.M.

Ballroom, Drake Hotel

"Rifles on the Firing Line." Charles C. Hillman, M.D., F.A.C.P., Brigadier General, Medical Corps, U. S. Army; Chief of Professional Service Division, Office of the Surgeon General, Washington, D. C.

"Syphilitic Heart Disease." James E. Paullin, M.D., F.A.C.P., President, American College of Physicians; President-Elect, American Medical Association; Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Ga.

"Aviation Medicine." Walter M. Boothby, M.D., F.A.C.P., Chairman, Mayo Aero Medical Unit, Rochester, Minn.

"The Problems of the Internist in the Navy." Robert E. Duncan, M.D., F.A.C.P. (by appointment), Captain, Medical Corps, U. S. Navy; Executive Officer, U. S. Naval Hospital, National Naval Medical Center, Bethesda, Md.

Intermission

"Medical Care of Aviation Personnel." David N. W. Grant, Brigadier General, Air Surgeon, Army Air Force, Washington, D. C.

"Cardiac Problems in War Time." Paul D. White, M.D., F.A.C.P., Physician, Massachusetts General Hospital, and Lecturer, Harvard Medical School, Boston, Mass.

"Shock." Warren H. Cole, M.D., F.A.C.S. (by invitation), Professor of Surgery and Head of the Department, University of Illinois College of Medicine, Chicago, Ill.

"Present Emergency." Frank V. Meriwether, M.D. (by appointment), Senior Surgeon, Director, U. S. Public Health Service, District No. 3, Chicago, Ill.

The Afternoon Session was followed by a social hour and cocktails in the Gold Coast Room of the Drake Hotel, followed by an informal dinner, at which Dr. LeRoy H. Sloan acted as Toastmaster. Brief addresses were made by Brigadier General C. C. Hillman (MC), U. S. Army, official envoy from the Office of the Surgeon General; Brigadier General David N. W. Grant, Air Surgeon of the U. S. Army Air Force, Washington, D. C.; Captain Robert E. Duncan (MC), U. S. Navy, official envoy of the Surgeon General of the Navy; Dr. Frank V. Meriwether, Senior Surgeon, U. S. Public Health Service, official envoy of the Surgeon General of that Service; Dr. James E. Paullin, Atlanta, Ga., President of the College; Dr. Ernest E. Irons, Chicago, President-Elect of the College; and Brigadier General John M. Willis (MC), U. S. Army, Commanding Officer, Camp Grant, Ill. Dr. Morris Fishbein, Editor of the Journal of the American Medical Association, made the principal address. Among distinguished guests introduced by the Toastmaster were: Dr. Cecil M. Jack, Decatur, A.C.P. Governor for southern Illinois; Dr. Robert M. Moore, Indianapolis, A.C.P. Governor for Indiana; Dr. B. F. Wolverton, Cedar Rapids, A.C.P. Governor for Iowa; Colonel Henry R. Carstens (MC), U. S. Army, A.C.P. Governor for Michigan; Dr. P. L. Ledwidge, Detroit, A.C.P. Acting Governor for Michigan; Dr. Elmer L. Sevringhaus, Madison, A.C.P. Governor for Wisconsin; Colonel Walter B. Martin (MC), U. S. Army, A.C.P. Governor for Virginia; Mr. E. R. Loveland, Philadelphia, Executive Secretary of the College; Captain Henry L. Dollard (MC), U. S. Navy, Commanding, Ninth Naval District, Great Lakes, Ill.; Captain William E. Eaton (MC), U. S. Navy, Commanding Officer, Great Lakes Naval Hospital; Dr. Paul D. White, Boston; Dr. Walter M. Boothby, Rochester, Minn.; Dr. Arthur R. Elliott, Chicago, former Regent of the College; Dr. James P. Simonds, Acting President of the Chicago Medical Society; Dr. Wilber E. Post, President, Chicago Institute of Medicine; Dr. Charles Phifer, Director, Office of Procurement and Assignment, Sixth Service Command, Chicago; Dr. Roscoe L. Sensenich, South Bend, Ind., Trustee of the American Medical Association; Dr. Malcolm T. MacEachern, Chicago, Associate Director of the American College of Surgeons; Dr. D. J. Davis, Dean, University of Illinois College of Medicine; Dr. J. Roscoe Miller, Dean, Northwestern University Medical School; and Dr. J. G. Powers, Acting Dean, Loyola University School of Medicine.

SPECIAL NOTICES

Office of War Information

War Production Board

Additional control over the purchase of laboratory equipment was put into effect by the issuance on December 5, 1942 of Limitation Order L–144, as amended.

The amended order provides that no purchaser of laboratory equipment shall be permitted to acquire an item valued at more than $50 or any quantity of the same item to the value of more than $50, without securing an authorization for such purchase from the Director General for Operations.

Application should be made on Form PD–620. Purchases authorized on the basis of this form will be assigned an AA–4 rating.

"Laboratory equipment" is defined in the order to mean material, instruments, appliances, devices, parts thereof, tools and operating supplies for laboratories, or for use in connection with operations usually carried on in laboratories, not including second-hand items.

The American Social Hygiene Association, Inc.

1790 Broadway, New York, N. Y.

Social Hygiene Day will take its battle stations throughout the country as in former years, despite the gasoline and rubber restrictions which are in force this year. Dr. Walter Clarke, Executive Director of the American Social Hygiene Association, in announcing the annual observance scheduled for Wednesday, February 3, 1943, said that this battle on the home front against venereal disease is nationwide and does not depend upon transportation to rally its fighting forces. Community meetings will take place throughout the land, sponsored by local clubs, church groups, and social and health agencies.

Last year, when tires and gas were not restricted, Social Hygiene Day was observed by thousands of public meetings, held in communities all over the United States, Dr. Clarke explained. He intimated that this number promises to be greatly increased in 1943, for the large meetings, serving metropolitan areas, will be supplemented by an even greater number of local meetings.

Dr. Clarke pointed out that in wartime more than ever the United States must man its battle stations in every city, town and hamlet, in order to stamp out the venereal diseases at their source. Syphilis and gonorrhea are enemies which threaten us at home. They disable our men at the front, but their roots are on the home front. For this reason Social Hygiene Day this year will assume a greater significance than ever before. It will be observed in every community, no matter how small it may be, by discussion of direct action designed to stamp out the two diseases which are as menacing to our armed forces as the bombs of our enemies.

"During the first world war, there were 157,146 more new cases of syphilis and gonorrhea among United States soldiers, sailors and marines," Dr. Clarke explained, "than there were wounds in battles. Total absences from duty due to this infection kept the equivalent of 20,600 men out of the fighting for a whole year, men trained for their country's service, men upon whom their country counted for its defense.

"In terms of today's hard held fronts such a loss would mean the equivalent of the personnel required to man five huge aircraft carriers and nine destroyers. No axis enemy could be more destructive than this enemy whom we must defeat on health battle fronts within our own country. We do not need to suffer this loss and do not need gas and tires to meet that enemy and to destroy him. We have the scientific weapons to prevent the spread of the venereal diseases. In war time the principal function of social hygiene organizations everywhere is to persuade every community to use these weapons effectively. Intelligent coöperation among the health and welfare agencies in every city and town will help stamp out venereal disease and thus help our armed forces to bring us victory on the battle fronts."

Postgraduate Course in Industrial Medicine and Hygiene Offered in Philadelphia

Under the auspices of The Philadelphia County Medical Society, directed by the Departments of Preventive Medicine and Public Health of the University of Pennsylvania and the Woman's Medical College of Pennsylvania, a Postgraduate Course in Industrial Medicine and Hygiene will be offered in Philadelphia for a period of eight weeks, beginning the first week in January. The classes will meet from 4:00 to 6:00 p.m. on Tuesdays, Thursdays and Saturdays, and the course will extensively cover the field. Copies of the program may be obtained by communicating directly with The Philadelphia County Medical Society.

FRIDAY AFTERNOON LECTURE SERIES—1942–43

At 4:30 o'clock

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street, New York City

1942

November 6: Disorders of the hypophysis from a clinical standpoint. David P. Barr, Professor of Medicine, Cornell Univ. Medical College.

November 13: Some recent advances in therapeutics, including the newer drugs of the sulfonamide group. Harry Gold, Assistant Professor, Department of Pharmacology, Cornell University Medical College.

November 20: The surgical treatment of circulatory disorders in the lower extremities, including diabetic gangrene. Gerald H. Pratt, Assistant Clinical Professor of Surgery, New York Post-Graduate Medical School, Columbia University.

December 4: The rôle of artificial insemination in treating human sterility. Alan F. Guttmacher, Associate Professor of Obstetrics, Johns Hopkins Medical School, Baltimore.

December 11: Virus pneumonia. Hobart A. Reimann, Professor of Medicine, Jefferson Medical College, Philadelphia.

December 18: Peritonitis, conservative treatment. Henry W. Cave, Assistant Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University.

1943

January 8: Present concepts and treatment of sinusitis. Russell C. Grove, Associate Otolaryngologist, Roosevelt Hospital.

January 15: Shoulder pain and disabilities. David M. Bosworth, Associate Attending Orthopedic Surgeon, St. Luke's Hospital.

January 22: Indications and contraindications for the newer anesthetic agents. Milton C. Peterson, Associate Professor of Anesthesia, New York Post-Graduate Medical School, Columbia University.

January 29: Modern treatment of the psychoses. S. Bernard Wortis, Professor of Psychiatry, New York University Medical College.

February 5: Intractable pain—surgical and medical treatment. Byron Stookey, Professor of Clinical Neurological Surgery, College of Physicians and Surgeons, Columbia University.

February 19: Clinical types of coronary insufficiency and their recognition. Robert L. Levy, Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University.

February 26: Recent advances in the clinical interpretation of laboratory data. Maurice Bruger, Associate Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University.

March 5: The rôle of the RH factor in erythroblastosis, transfusion accidents, and its importance to the obstetrician. Philip Levine, Bacteriologist to the Newark Beth Israel Hospital, Newark.

March 12: Toxemias of pregnancy. Albert H. Aldridge, Chief Surgeon, Woman's Hospital.

March 19: Brucellosis: diagnosis, differential diagnosis and treatment. Harold J. Harris, Lieut. Commander, (MC) USNR.

March 26: Rheumatoid arthritis and its treatment, including gold therapy. M. Henry Dawson, Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University.

April 2: Postcholecystectomy syndrome. Ralph Colp, Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University.

April 9: Phosphatase values in relation to bone diseases. Henry L. Jaffe, Director of Laboratories, Hospital for Joint Diseases.

April 16: Value of roentgen therapy in inflammatory conditions. Maurice Lenz, Professor of Clinical Radiology, College of Physicians and Surgeons, Columbia University.

NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 13, 1942, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

Elections to Fellowship

December 13, 1942

Fellowship Candidates	*Sponsors*
Arizona	
Leslie Rest Kober, Phoenix	Howell Randolph, Earle W. Phillips, Fred G. Holmes
Hilton John McKeown, Phoenix	Robert S. Flinn, Frank J. Milloy, Fred G. Holmes
Arkansas	
John Nye Compton, Little Rock	Silas C. Fulmer, Paul C. Eschweiler, Oliver C. Melson
California	
Kendall Bennett Holmes, Fresno	W. E. Richard Schottstaedt, Ernest B. Bradley, Ernest H. Falconer
Walter Charles Smallwood, Long Beach	Burrell O. Raulston, Howard F. West, Roy E. Thomas
Francis Marion Pottenger, Jr., Monrovia	Willard J. Stone, Egerton L. Crispin, Roy E. Thomas
Edward Carl Rosenow, Jr., Pasadena	Willard J. Stone, Burrell O. Raulston, Roy E. Thomas
Colorado	
Clarke Horace Barnacle, Denver (M.R.C., U.S.A.)	Ward Darley, Jr., Charles S. Bluemel, James J. Waring
Robert Todd Terry, Denver (M.R.C., U.S.A.)	W. Bernard Yegge, Ward Darley, Jr., James J. Waring
Connecticut	
Edward Gipstein, New London	Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington
William Harold Weidman, Norwich	Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington
James Roby Gudger, West Hartford (M.C., U.S.N.R.)	Alvin E. Murphy, Harold J. Stewart, Charles H. Turkington
District of Columbia	
General Profession	
Harry Filmore Dowling, Washington	Walter K. Myers, George R. Minot, Wallace M. Yater

Fellowship Candidates	*Sponsors*
MEDICAL CORPS, U. S. NAVY	
Ladislaus Louis Adamkiewicz, Portland, Maine	Donald H. Daniels, Mortimer Warren, Ross T. McIntire
Gordon Bennett Tayloe, Philadelphia, Pa.	Ross T. McIntire
U. S. PUBLIC HEALTH SERVICE	
Mason Victor Hargett, Hamilton, Mont.	Ferdinand R. Schemm, Ernest D. Hitchcock, Thomas Parran
Frederick Andrew Johansen, Carville, La.	Thomas Parran
FLORIDA	
Rollin David Thompson, Orlando	Meredith Mallory, Spencer A. Folsom, Turner Z. Cason
GEORGIA	
Arthur Park McGinty, Atlanta (M.C., U.S.N.R.)	Evert A. Bancker, Mason I. Lowance, Glenville Giddings
ILLINOIS	
Arthur Seldon Mann, Alton (M.R.C., U.S.A.)	V. Thomas Austin, Charles H. Drenckhahn, Cecil M. Jack
Richard Brooks Capps, Chicago (M.R.C., U.S.A.)	George H. Coleman, Fred E. Ball, LeRoy H. Sloan
Gilbert Henry Marquardt, Chicago	James G. Carr, Alexander A. Goldsmith, LeRoy H. Sloan
Theodore Robert Van Dellen, Chicago (M.R.C., U.S.A.)	J. Roscoe Miller, James G. Carr, LeRoy H. Sloan
George Clarence Turnbull, Evanston (M.R.C., U.S.A.)	Samuel J. Lang, James G. Carr, LeRoy H. Sloan
Eugene Lawrence Walsh, Evanston (M.R.C., U.S.A.)	J. Roscoe Miller, Laurence E. Hines, LeRoy H. Sloan
John Edward McCorvie, Peoria	Harry A. Durkin, George Parker, Cecil M. Jack
William Joseph Bryan, Rockford	Henry C. Sweany, Karl J. Henrichsen, Cecil M. Jack
Richard Fleetwood Herndon, Springfield	George B. Stericker, Samuel E. Munson, Cecil M. Jack
Arthur Sterling Webb, Wheaton	Walter H. Watterson, Josiah J. Moore, LeRoy H. Sloan
INDIANA	
Arthur B. Richter, Indianapolis	James O. Ritchey, Edgar F. Kiser, Robert M. Moore
IOWA	
Willis Marion Fowler, Iowa City	Fred M. Smith, John C. Parsons, Benjamin F. Wolverton
James Alexander Greene, Iowa City	Fred M. Smith, John C. Parsons, Benjamin F. Wolverton
Horace Marshall Korns, Iowa City	Fred M. Smith, John C. Parsons, Benjamin F. Wolverton
KANSAS	
Clarence Wilber Erickson, Pittsburg (M.R.C., U.S.A.)	Thomas T. Holt, Fred J. McEwen, Harold H. Jones
LOUISIANA	
Joseph Steven D'Antoni, New Orleans	John H. Musser, Grace A. Goldsmith, Joseph E. Knighton

Fellowship Candidates	*Sponsors*
Chester Sebastian Fresh, New Orleans (M.R.C., U.S.A.)	Edgar Hull, Joseph O. Weilbaecher, Jr., Joseph E. Knighton
Manuel Gardberg, New Orleans	Allan Eustis, Randolph Lyons, Joseph E. Knighton
MARYLAND	
Charles Henry Conley, Jr., Buckeystown (M.C., U.S.N.R.)	Henry M. Hensen, Sydney R. Miller, Wetherbee Fort
MASSACHUSETTS	
Thomas Hale Ham, Boston	George R. Minot, Chester S. Keefer, William B. Breed
Lester Dow Watson, Milton	Chester S. Keefer, John A. Foley, William B. Breed
Allen Gilbert Brailey, Newton Highlands (M.C., U.S.N.R.)	Greene FitzHugh, Maurice Fremont-Smith, William B. Breed
Hugh Francis Folsom, Southborough	James H. Means, Paul D. White, William B. Breed
MICHIGAN	
John McFarland Sheldon, Ann Arbor (M.R.C., U.S.A.)	Cyrus C. Sturgis, Herman H. Riecker, Douglas Donald
Abraham Becker, Detroit (M.R.C., U.S.A.)	Solomon G. Meyers, Douglas Donald, Patrick L. Ledwidge
Nelson Wright Diebel, Detroit	George B. Hoops, Rollin H. Stevens, Henry R. Carstens
Benjamin Juliar, Detroit (M.R.C., U.S.A.)	Emmet F. Pearson, Gordon B. Myers, Harry L. Arnold, Patrick L. Ledwidge
Mark Ronald McQuiggan, Detroit	Louis J. Bailey, John A. Hookey, Patrick L. Ledwidge
Max Karl Newman, Detroit	George B. Hoops, Curt P. Schneider, Patrick L. Ledwidge
Louis John Steiner, Detroit	Frank J. Sladen, John G. Mateer, Patrick L. Ledwidge
Gordon Wesley Balyeat, Grand Rapids (M.C., U.S.N.R.)	Joseph B. Whinery, Sumner M. Wells, Jr., Patrick L. Ledwidge
Benjamin Bismark Blum, Petoskey	Edgar V. Allen, Floyd H. Lashmet, Douglas Donald
Cleo Russel Gatley, Pontiac (M.R.C., U.S.A.)	Harold R. Roehm, George A. Sherman, Patrick L. Ledwidge
Evert Waitman Meredith, Port Huron	Frank J. Sladen, F. Janney Smith, Douglas Donald
Bernard Alec Watson, Three Oaks (M.R.C., U.S.A.)	Martin A. Mortensen, Lloyd E. Verity, Cyrus C. Sturgis, Douglas Donald
MINNESOTA	
Alphonse Edmund Walch, Minneapolis	Edwin L. Gardner, Ragnvald S. Ylvisaker, Edward H. Rynearson
MISSOURI	
Michael Bernreiter, Kansas City (M.R.C., U.S.A.)	Samuel H. Snider, Frank I. Ridge, A. Comingo Griffith
MONTANA	
Charles Francis Little, Great Falls	Ferdinand R. Schemm, Harold W. Gregg, Ernest D. Hitchcock
Meredith Benjamin Hesdorffer, Missoula (U.S.P.H.S., R.)	Allen R. Foss, Archie L. Gleason, Ernest D. Hitchcock
NEBRASKA	
Orange Van Calhoun, Lincoln	Floyd L. Rogers, John C. Thompson, Warren Thompson

Fellowship Candidates	*Sponsors*
New Jersey	
Frederick Hnat, Elizabeth (M.R.C., U.S.A.)	Horace R. Livengood, Michael Vinciguerra, George H. Lathrope
Joseph Joel Labow, Elizabeth	Arturo R. Casilli, Harry Bloch, George H. Lathrope
Jesse McCall, Newton (M.R.C., U.S.A.)	George J. Young, Harold S. Hatch, George H. Lathrope
New York	
Benjamin Burbank, Brooklyn (M.R.C., U.S.A.)	J. Hamilton Crawford, Tasker Howard, C. F. Tenney
Louis Friedfeld, Brooklyn (M.R.C., U.S.A.)	Charles Shookhoff, William Goldring, Asa L. Lincoln
Irving Greenfield, Brooklyn (M.R.C., U.S.A.)	Tasker Howard, Irving Gray, C. F. Tenney
Arthur Gerson Hollander, Brooklyn (M.R.C., U.S.A.)	J. Hamilton Crawford, William H. Lohman, Asa L. Lincoln
Aaron Arnold Karan, Brooklyn	Morris M. Banowitch, Isaac Gerber, Asa L. Lincoln
Abraham M. Litvak, Brooklyn	Maurice J. Dattelbaum, Jean A. Curran, C. F. Tenney
Samuel Millman, Brooklyn (M.R.C., U.S.A.)	Simon R. Blatteis, Irving J. Sands, Asa L. Lincoln
Abraham Max Rabiner, Brooklyn	Orman C. Perkins, Tasker Howard, Asa L. Lincoln
Bernard Seligman, Brooklyn	Henry M. Feinblatt, Tasker Howard, C. F. Tenney
John James Weber, Brooklyn	Alexis T. Mays, William A. Lange, C. F. Tenney
Edgar Coleman Beck, Buffalo	Allen A. Jones, Abraham H. Aaron, Nelson G. Russell
Walter David Westinghouse, Buffalo	Stuart L. Vaughan, Francis E. Kenny, Nelson G. Russell
George Miner Mackenzie, Cooperstown	Robert F. Loeb, Randolph West, Walter W. Palmer, C. F. Tenney
Michael Bevilacqua, Glendale (M.R.C., U.S.A.)	Frank R. Mazzola, Goodwin A. Distler, Asa L. Lincoln
James Burnett Shields, Glens Falls	Morris Maslon, George A. Chapman, Asa L. Lincoln
Henry Craig Fleming, New York	Russell L. Cecil, Arthur F. Chace, Asa L. Lincoln
Herman Louis Frosch, New York	Nathan B. Van Etten, Isidore W. Held, C. F. Tenney
William Alden Gardner, New York	Robert F. Loeb, Randolph West, Walter W. Palmer, Asa L. Lincoln
Samuel Waldron Lambert, Jr., New York	Robert F. Loeb, Franklin M. Hanger, Walter W. Palmer, C. F. Tenney
Mack Lipkin, New York	Walter G. Lough, Carl H. Greene, Asa L. Lincoln
Aaron Edwin Margulis, New York	Max Pinner, J. Burns Amberson, Jr., C. F. Tenney
Carl Muschenheim, New York	Claude E. Forkner, Harold G. Wolff, Asa L. Lincoln
Eli Hyman Rubin, New York	Max Pinner, David Marine, Asa L. Lincoln
Gamliel Saland, New York	Irving J. Sands, H. Rawle Geyelin, Asa L. Lincoln
Frederick William Williams, New York	Herman O. Mosenthal, James R. Scott, Asa L. Lincoln
John Winthrop Pennock, Syracuse, N. Y. (M.R.C., U.S.A.)	William A. Groat, Edward C. Reifenstein, Nelson G. Russell
Ranald Edwards Mussey, Troy	Stephen H. Curtis, Crawford R. Green, Asa L. Lincoln
Harold Jerome Harris, Westport (M.C., U.S.N.R.)	Stanton Tice Allison, James L. McCartney, Asa L. Lincoln

Fellowship Candidates	*Sponsors*
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Joseph John Combs, Raleigh	Hubert B. Haywood, William B. Dewar, Paul F. Whitaker
Thomas Leonard Umphlet, Raleigh	Verne S. Caviness, Hubert B. Haywood, Paul F. Whitaker
Ohio	
Ellis Herndon Hudson, Athens (M.C., U.S.N.R.)	Calvus E. Richards, Charles A. Doan, A. B. Brower
Sander Cohen, Cincinnati (M.R.C., U.S.A.)	Hiram B. Weiss, Robert C. Rothenberg, A. B. Brower
Charles Kenneth Riddle, Cincinnati	John H. Skavlem, David A. Tucker, Jr., A. B. Brower
William Parrish Garver, Cleveland	John A. Toomey, Harold Feil, Ray W. Kissane, A. B. Brower
McKinley London, Cleveland (M.C., U.S.N.R.)	Vernon C. Rowland, Charles T. Way, A. B. Brower
Mortimer Lee Siegel, Cleveland	Samuel S. Berger, Roy W. Scott, A. B. Brower
Francis Joseph Heringhaus, Mansfield (M.R.C., U.S.A.)	Roy W. Scott, Theodore L. Bliss, A. B. Brower
Raymond John Borer, Toledo (M.R.C., U.S.A.)	Frank C. Clifford, John T. Murphy, A. B. Brower
Charles Harry Warnock, Youngstown	Colin R. Clark, William H. Bunn, A. B. Brower
Oklahoma	
William Turner Bynum, Chickasha	Philip M. McNeill, Wann Langston, Lea A. Riely
James Floyd Moorman, Oklahoma City	Joseph T. Martin, Hull W. Butler, Lea A. Riely
Oregon	
Edmund Henry Berger, Portland (M.C., U.S.N.R.)	Marr Bisaillon, John H. Fitzgibbon, Homer P. Rush
Donald Edgar Forster, Portland (M.R.C., U.S.A.)	Edwin E. Osgood, David W. E. Baird, Homer P. Rush
Howard Phelps Lewis, Portland (M.R.C., U.S.A.)	John H. Fitzgibbon, Marr Bisaillon, Homer P. Rush
Pennsylvania	
Allen Wilson Cowley, Harrisburg	Carl E. Ervin, Charles C. Wolferth, Edward L. Bortz
Harvey Holmes Seiple, Lancaster	Roland N. Klemmer, Samuel S. Simons, Edward L. Bortz
George Warren Burnett, Oil City	Kelse M. Hoffman, Harvey M. Watkins, R. R. Snowden
Andrew Wirt Goodwin, Oil City	Harvey M. Watkins, C. Howard Marcy, R. R. Snowden
Jack Edward Berk, Philadelphia (M.R.C., U.S.A.)	Henry L. Bockus, Martin E. Rehfuss, Edward L. Bortz
Julius Hiram Comroe, Jr., Philadelphia	Simon S. Leopold, T. Grier Miller, Edward L. Bortz
William Wallace Dyer, Philadelphia	Edward S. Dillon, Thomas Fitz-Hugh, Jr., Edward L. Bortz
Kendall Adams Elsom, Philadelphia (M.R.C., U.S.A.)	T. Grier Miller, Charles C. Wolferth, O. H. Perry Pepper, Edward L. Bortz
John Quintin Griffith, Jr., Philadelphia	Charles C. Wolferth, T. Grier Miller, Edward L. Bortz
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South Carolina	
Albert May Eaddy, Columbia	J. Heyward Gibbes, Hugh Smith, Kenneth M. Lynch

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Bergein Marion Overholt, Knoxville (M.R.C., U.S.A.)	Daniel R. Thomas, Robert B. Wood, J. O. Manier, William C. Chaney
TEXAS	
William Ladelle Howell, Fort Worth (M.R.C., U.S.A.)	Truman C. Terrell, May Owen, M. D. Levy
Flavius Downs Mohle, Houston (M.R.C., U.S.A.)	Alvis E. Greer, Henry N. Gemoets, M. D. Levy
Edwin G. Faber, Tyler (M.R.C., U.S.A.)	H. Frank Carman, David W. Carter, Jr., M. D. Levy
Emory Dallas Hollar, Vernon	Truman C. Terrell, Oliver B. Kiel, M. D. Levy
UTAH	
Lloyd Lorenzo Cullimore, Provo	Ivan Thompson, Fuller B. Bailey, Louis E. Viko
VIRGINIA	
James Porter Baker, Richmond (M.R.C., U.S.A.)	Douglas G. Chapman, T. Dewey Davis, Walter B. Martin
Nathan Bloom, Richmond	Harry Walker, Douglas G. Chapman, Walter B. Martin
WASHINGTON	
Harold Julian Gunderson, Everett (M.R.C., U.S.A.)	George D. Capaccio, Lester J. Palmer, Edwin G. Bannick
Eric MacMillan Chew, Seattle (M.R.C., U.S.A.)	Lester J. Palmer, George D. Capaccio, Edwin G. Bannick
Clark Cleo Goss, Seattle (M.C., U.S.N.R.)	James E. Hunter, Homer Wheelon, Edwin G. Bannick
WEST VIRGINIA	
John Pierpont Helmick, Fairmont	Charles W. Waddell, J. Lewis Blanton, Albert H. Hoge
WISCONSIN	
Adolph Matthew Hutter, Fond du Lac	Karver L. Puestow, Chester M. Kurtz, Elmer L. Sevringhaus
M. Meredith Baumgartner, Janesville	Vincent W. Koch, Thomas O. Nuzum, Elmer L. Sevringhaus
Ruth Caldwell Foster, Madison	Chester M. Kurtz, Joseph S. Evans, Elmer L. Sevringhaus
Edgar Stillwell Gordon, Madison (M.R.C., U.S.A.)	Joseph S. Evans, Marie L. Carns, Elmer L. Sevringhaus
Ovid Otto Meyer, Madison	Joseph S. Evans, Harold M. Coon, Elmer L. Sevringhaus
Kenneth Paul Hoel, Pewaukee	Harold M. Coon, Llewellyn R. Cole, Elmer L. Sevringhaus
Harold Herman Fechtner, Wausau	William S. Middleton, Joseph S. Evans, Elmer L. Sevringhaus
TERRITORY OF HAWAII	
Henry Costill Gotshalk, Honolulu	Nils P. Larsen, Stewart E. Doolittle, Harry L. Arnold
DOMINION OF CANADA	
Alberta	
Harold Orr, Edmonton	Maxwell M. Cantor, John W. Scott, George F. Strong
Manitoba	
Francis Alexander Lavens Mathewson, Winnipeg (R.C.A.F.)	Fred Cadham, John M. McEachern, George F. Strong

Fellowship Candidates	*Sponsors*
Charles Hutchinson A'Court Walton, Winnipeg (R.C.A.M.C.)	Fred Cadham, J. Currie McMillan, George F. Strong

"RESOLVED, that the following list of 7 be and herewith are elected to Fellowship in the American College of Physicians as of March 31, 1943":

DISTRICT OF COLUMBIA

MEDICAL CORPS, U. S. ARMY

Hugh Richmond Gilmore, Jr., Fort Sheridan, Ill.	James C. Magee
Neely Cornelius Mashburn, Ellington Field, Tex.	James C. Magee

ILLINOIS

Howard Avery Lindberg, Chicago (M.R.C., U.S.A.)	M. Herbert Barker, J. Roscoe Miller, LeRoy H. Sloan

NEW YORK

Roger Sherman Mitchell, Jr., Glens Falls	Carl R. Comstock, William H. Ordway, Asa L. Lincoln
Robert Collier Page, New York (M.R.C., U.S.A.)	Willard J. Denno, Thomas Klein, Asa L. Lincoln

PENNSYLVANIA

Leon Schwartz, Philadelphia (U.S.P.H.S., R.)	Harrison F. Flippin, William E. Robertson, Edward L. Bortz

WISCONSIN

George Colville Owen, Oshkosh (M.R.C., U.S.A.)	Oscar Lotz, Alfred W. Gray, Elmer L. Sevringhaus

ELECTIONS TO ASSOCIATESHIP

December 13, 1942

Associateship Candidates	*Sponsors*
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Ivan Columbus Berrey, Birmingham	Joseph E. Hirsh, James S. McLester, Fred Wilkerson
John Day Peake, Mobile	Grady O. Segrest, Joseph H. Little, Fred Wilkerson
Justus MacIlwaine Barnes, Montgomery (M.R.C., U.S.A.)	J. Harold Watkins, James F. Alison, Fred Wilkerson
ARIZONA	
Kent Hanthorn Thayer, Phoenix (M.R.C., U.S.A.)	George F. Aycock, Daniel B. Faust, James J. Waring
CALIFORNIA	
Earl Bryning Ray, Belleflower (M.R.C., U.S.A.)	Daniel D. Comstock, E. Richmond Ware, Roy E. Thomas
Ephraim Philip Engleman, Fresno (M.R.C., U.S.A.)	Stacy R. Mettier, H. Clare Shepardson, Ernest H. Falconer
Otto Arndal, Glendale	R. Manning Clarke, Eugene L. Armstrong, Roy E. Thomas
James Hallam Cope, Jr., Livermore	Chesley Bush, Benjamin W. Black, Ernest H. Falconer
Lewis Thomas Bullock, Los Angeles	Donald J. Frick, Arthur S. Granger, Roy E. Thomas
John Langdon Gompertz, Piedmont (M.R.C., U.S.A.)	Chesley Bush, Benjamin W. Black, Ernest H. Falconer
William Dustin Evans, Santa Barbara (M.R.C., U.S.A.)	William P. Corr, Franklin R. Nuzum, Roy E. Thomas

Associateship Candidates	*Sponsors*
Walter Patrick Martin, Santa Barbara (M.R.C., U.S.A.)	William P. Corr, Ernest M. Hall, Roy E. Thomas
Lorenz McBurney Waller, Santa Barbara (M.R.C., U.S.A.)	William P. Corr, William C. Boeck, Roy E. Thomas

COLORADO

Karl Frederick Arndt, Denver (M.R.C., U.S.A.)	Alfred M. Wolfe, Edward G. Billings, James J. Waring
Frank Bartlett McGlone, Denver (M.R.C., U.S.A.)	George F. Aycock, Daniel B. Faust, James J. Waring
Arthur C. Rest, Spivak	A. Lee Briskman, Bernardine T. McMahon, James J. Waring

CONNECTICUT

Lawrence Shapiro Ward, New London	Louis H. Nahum, Barnett Greenhouse, Charles H. Turkington

DELAWARE

Constance Anthony D'Alonzo, Wilmington (M.R.C., U. S. A.)	George H. Gehrmann, John H. Foulger, Lewis B. Flinn

DISTRICT OF COLUMBIA

General Profession

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Ernest Quong King, Washington (M.R.C., U.S.A.)	Karl W. Brimmer, Russell M. Wilder, Wallace M. Yater
Lawrence Elias Putnam, Washington	Theodore G. Klumpp, Walter A. Bloedorn, Wallace M. Yater

MEDICAL CORPS, U. S. NAVY

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George Neely Raines, Bethesda, Md.	Robert E. Duncan, Arthur M. Master, Ross T. McIntire
Fitz-John Weddell, Jr., Washington, D. C.	Clyde W. Brunson, Albert G. Bower, Ross T. McIntire

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Irving Donald Fagin, Detroit, Mich.	Alpheus F. Jennings, Samuel S. Altshuler, Patrick L. Ledwidge, Thomas Parran
Carl Jacob Kornreich, Staten Island, N. Y.	Arthur C. DeGraff, Thomas Parran

FLORIDA

Elwyn Evans, Winter Park	Kenneth Phillips, Spencer A. Folsom, Turner Z. Cason

GEORGIA

Harry Parks, Atlanta (M.R.C., U.S.A.)	Joseph Yampolsky, R. Hugh Wood, Glenville Giddings
Joseph Alvin Leaphart, Jesup	James C. Metts, J. Reid Broderick, Glenville Giddings
Charles Bennett Fulghum, Sr., Milledgeville	Thomas L. Ross, Jr., Harold C. Atkinson, Glenville Giddings

ILLINOIS

Clarence Edward Merkle, Alton	Ralph A. Kinsella, Joseph F. Bredeck, Cecil M. Jack
Arthur Bernstein, Chicago	Sidney A. Portis, Aaron Arkin, LeRoy H. Sloan
Herman Felix DeFeo, Chicago	Italo F. Volini, Leo L. Hardt, LeRoy H. Sloan
Joseph Charles Ehrlich, Chicago (M.R.C., U.S.A.)	Robert W. Keeton, Italo F. Volini, LeRoy H. Sloan

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Carl August Johnson, Chicago	Arthur R. Elliott, Grant H. Laing, LeRoy H. Sloan
Clayton Jackson Lundy, Chicago (M.R.C., U.S.A.)	Lee C. Gatewood, Willard O. Thompson, LeRoy H. Sloan
Hugh Barrett O'Neil, Chicago	M. Herbert Barker, J. Roscoe Miller, LeRoy H. Sloan
Carl Otto Rinder, Chicago	Arthur R. Elliott, Joseph A. Capps, LeRoy H. Sloan
Irving Elihu Steck, Chicago	Robert W. Keeton, George E. Wakerlin, LeRoy H. Sloan
Solomon Carl Werch, Chicago	Andrew C. Ivy, Alexander A. Goldsmith, LeRoy H. Sloan
Ralph Waldo Trimmer, Oak Park	Willard O. Thompson, Lee C. Gatewood, LeRoy H. Sloan
Howard Dick Countryman, Rockford (M.R.C., U.S.A.)	Clarence H. Boswell, Harold D. Palmer, LeRoy H. Sloan
Arvid Theodore Johnson, Rockford	Walter L. Palmer, Willard O. Thompson, LeRoy H. Sloan
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Morris Caplinger Thomas, Indianapolis (M.R.C., U.S.A.)	Frank L. Jennings, Harold C. Ochsner, Robert M. Moore
IOWA	
Julian Ecwart McFarland, Ames	John H. Peck, John C. Parsons, Benjamin F. Wolverton
Edward Sumner Brewster, Boone (M.R.C., U.S.A.)	Walter L. Bierring, John C. Parsons, Fred M. Smith, Benjamin F. Wolverton
George Elmer Mountain, Des Moines	Harry L. Smith, Philip W. Brown, Edgar V. Allen, Benjamin F. Wolverton
KANSAS	
Earl Saxe, Topeka (M.R.C., U.S.A.)	William C. Menninger, James G. Stewart, Harold H. Jones
Frederic Wilhelm Hall, Winfield (M.R.C., U.S.A.)	George A. Westfall, Daniel V. Conwell, Harold H. Jones
LOUISIANA	
John Samuel LaDue, New Orleans	Robert H. Bayley, Louis A. Monte, Edgar Hull
George Rodney Meneely, New Orleans	Edgar Hull, William S. McCann, Joseph E. Knighton
Leonard Collier Paggi, New Orleans	Louis A. Monte, Robert H. Bayley, Edgar Hull
Paul Jasper Thomas, New Orleans	John H. Musser, Grace A. Goldsmith, Edgar Hull
Lee Williamson, New Orleans (M.R.C., U.S.A.)	Edgar Hull, Joseph O. Weilbaecher, Jr., Joseph E. Knighton
MASSACHUSETTS	
David Sydney Sherman, Brookline	James M. Faulkner, John A. Foley, William B. Breed
MICHIGAN	
Gerald Norman Rein, Benton Harbor	John V. Fopeano, John D. Littig, Henry R. Carstens
Raymond Kenneth Bartholomew, Detroit	Frank J. Sladen, Frank R. Menagh, Douglas Donald
Henry Alexander Bradford, Detroit (M.R.C., U.S.A.)	F. Janney Smith, Frank J. Sladen, Douglas Donald
Louis Sanderson Lipschutz, Detroit (M.R.C., U.S.A.)	Rudolf Leiser, Louis J. Bailey, Patrick L. Ledwidge
James Murdock MacMillan, Detroit	Frank J. Sladen, John G. Mateer, Patrick L. Ledwidge

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Harris Vincent Lilga, Petoskey	Floyd H. Lashmet, Russell L. Haden, Douglas Donald
MINNESOTA	
Royal V. Sherman, Red Wing	Jay C. Davis, Archibald E. Cardle, Edward H. Rynearson
Lawrence Harvey Beizer, Rochester (M.R.C., U.S.A.)	Herbert Z. Giffin, Charles H. Watkins, Edgar V. Allen
John Daniel Call, Rochester	David M. Berkman, Arlie R. Barnes, Edward H. Rynearson
Thornton Tayloe Perry, III, Rochester (M.R.C., U.S.A.)	Nelson W. Barker, Edgar A. Hines, Jr., Edgar V. Allen
MISSOURI	
Joseph Henry Delaney, Columbia (M.R.C., U.S.A.)	Dan G. Stine, William B. Brown, Ralph Kinsella
Louis Aloysius Scarpellino, Kansas City	Peter T. Bohan, Paul F. Stookey, Ralph Kinsella
Edward Massie, St. Louis	David M. Skilling, Jr., Harry L. Alexander, Ralph Kinsella
NEBRASKA	
Charles Edward Thompson, Omaha	Rodney W. Bliss, George P. Pratt, Warren Thompson
NEW JERSEY	
Levi Moore Walker, Atlantic City (M.R.C., U.S.A.)	Hilton S. Read, Samuel L. Salasin, George H. Lathrope
Samuel Thomas Busansky, Browns Mills	Marcus W. Newcomb, Martin H. Collier, George H. Lathrope
Richard Wagner, Elizabeth (M.R.C., U.S.A.)	Arturo R. Casilli, Harry Bloch, George H. Lathrope
Cornelius C. Perrine, Fair Haven	Frank J. Altschul, Carlos A. Pons, George H. Lathrope
Alfred Leon Kruger, Jersey City (M.R.C., U.S.A.)	Abraham E. Jaffin, Berthold S. Pollak, George H. Lathrope
Ralph Miller, Newark	Aaron E. Parsonnet, Jerome G. Kaufman, George H. Lathrope
NEW YORK	
Walter Kent Van Alstyne, Binghamton	Ralph J. McMahon, George C. Hamilton, Nelson G. Russell, Asa L. Lincoln
Charles John Crawley, Brooklyn	Alexis T. Mays, William A. Lange, C. F. Tenney
Isidore Albert Feder, Brooklyn (M.R.C., U.S.A.)	Maurice J. Dattelbaum, Irving J. Sands, Asa L. Lincoln
Victor Grover, Brooklyn	Edwin P. Maynard, Jr., William H. Lohman, Asa L. Lincoln
Saul Michalover, Brooklyn (M.R.C., U.S.A.)	Benjamin M. Eis, Irving J. Sands, Asa L. Lincoln
Israel Abraham Schiller, Brooklyn (M.R.C., U.S.A.)	Irving J. Sands, Herbert R. Edwards, Asa L. Lincoln
David Hale Clement, Buffalo	Allen A. Jones, Abraham H. Aaron, Nelson G. Russell
Jay Ignatius Evans, Buffalo	Allen A. Jones, Abraham H. Aaron, Nelson G. Russell
Edward Royal Henry Kurz, Glendale	John G. Senese, William H. Lohman, Asa L. Lincoln
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Selian Hebald, New York	Robert A. Cooke, Robert Chobot, Asa L. Lincoln
Scott Johnson, New York	Walter P. Anderton, James Alex. Miller, Asa L. Lincoln
Leon Lewis, New York	Asa L. Lincoln, Robert M. Lintz, C. F. Tenney
George Charles Linn, New York	Robert F. Loeb, Frederick R. Bailey, Walter W. Palmer, Asa L. Lincoln
Samuel Melamed, New York	David Marine, Bernard S. Oppenheimer, Asa L. Lincoln
Robert Anton Newburger, New York (M.R.C., U.S.A.)	Bernard S. Oppenheimer, Norman Jolliffe, C. F. Tenney
Albert Christy Santy, New York	Howard F. Shattuck, Arthur J. Antenucci, Asa L. Lincoln
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Louis Julius Soffer, New York	Bernard S. Oppenheimer, George Baehr, C. F. Tenney
Saul L. Solomon, New York (M.R.C., U.S.A.)	Louis F. Bishop, Jr., Herman O. Mosenthal, C. F. Tenney
Morris Feldman Steinberg, New York	Bernard S. Oppenheimer, Solomon Silver, C. F. Tenney
Arthur Mandel Tunick, New York (M.R.C., U.S.A.)	I. Ogden Woodruff, Isidore W. Held, C. F. Tenney
Roy Elias Kinsey, Peekskill (M.R.C., U.S.A.)	Paul W. Clough, Thurman D. Kitchin, Asa L. Lincoln
Maurice Anthony Donovan, Schenectady	Lester Betts, Isaac Shapiro, C. F. Tenney
Harry E. Reynolds, Schenectady	Lester Betts, Isaac Shapiro, Asa L. Lincoln
John Marcus Rice, Watertown	William W. Hall, Walter F. Smith, Nelson G. Russell
Ohio	
John Harold Kotte, Cincinnati	Johnson McGuire, Hubert H. Shook, A. B. Brower
Edward Allen Marshall, Cleveland (M.R.C., U.S.A.)	Joseph C. Placak, Milton B. Cohen, A. B. Brower
Oscar Ferdinand Rosenow, Columbus	Ray W. Kissane, Herbert V. Weirauk, Louis Mark, A. B. Brower
Frank William Anzinger, Springfield (M.R.C., U.S.A.)	Carl H. Reuter, Benedict Olch, A. B. Brower
David Lynn Beers, Warren	Leo C. Bean, Colin R. Clark, A. B. Brower
Harold Ellsworth Hathhorn, Youngstown (M.R.C., U.S.A.)	Morris Deitchman, William H. Bunn, A. B. Brower
Oklahoma	
Frank Thomas Joyce, Chickasha (M.R.C., U.S.A.)	Lewis J. Moorman, Philip M. McNeill, Lea A. Riely
Charles Edwards Leonard, Oklahoma City	Coyne H. Campbell, F. Redding Hood, Lea A. Riely
Pennsylvania	
Frederic William Wilson, Franklin	Harvey M. Watkins, Kelse M. Hoffman, R. R. Snowden
Ross Kennedy Childerhose, Harrisburg	Constantine P. Faller, Frank F. D. Reckord, Edward L. Bortz
Carl Cooke Hoffman, II, Harrisburg (M.R.C., U.S.A.)	Constantine P. Faller, Carl E. Ervin, Edward L. Bortz
Robert Alexander Houston, Harrisburg	Carl E. Ervin, Constantine P. Faller, Edward L. Bortz
Bernard J. McCloskey, Johnstown	Horace B. Anderson, Laurrie D. Sargent, R. R. Snowden
Samuel Baer, Philadelphia	Harold L. Goldburgh, Joseph C. Doane, Edward L. Bortz

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Edward Bernard LeWinn, Philadelphia	Mitchell Bernstein, Joseph C. Doane, Edward L. Bortz
Pascal Francis Lucchesi, Philadelphia	Rufus S. Reeves, Stanley P. Reimann, Edward L. Bortz
James Edwin Pugh, Philadelphia	George C. Griffith, Joseph T. Beardwood, Jr., Edward L. Bortz
Mayer Albert Green, Pittsburgh	Harry M. Margolis, Milton Goldsmith, R. R. Snowden
Joseph Edward Harenski, Pittsburgh	Frederick B. Utley, C. Howard Marcy, R. R. Snowden
Andrew James Parker, Pittsburgh	Frederick B. Utley, C. Howard Marcy, R. R. Snowden
RHODE ISLAND	
Alphonse William Lupoli, Warwick	William S. Streker, James Hamilton, Alex. M. Burgess
TENNESSEE	
James Warrie McElroy, Memphis (M.R.C., U.S.A.)	Whitman Rowland, William C. Colbert, William C. Chaney
TEXAS	
Carl Norman Giere, El Paso	Orville E. Egbert, James J. Gorman, M. D. Levy
John Buckley Fershtand, Fort Worth	Will S. Horn, Caleb O. Terrell, M. D. Levy
Lester Conrad Feener, Harlingen (M.R.C., U.S.A.)	Sam E. Thompson, Joseph Kopecky, M. D. Levy
Charles Dickens Reece, Houston	Frederick R. Lummis, Homer E. Prince, M. D. Levy
UTAH	
Theodore Charles Bauerlein, Salt Lake City	G. Gill Richards, William C. Walker, Louis E. Viko
VIRGINIA	
Byrd Stuart Leavell, Charlottesville	Eugene M. Landis, Henry B. Mulholland, Walter B. Martin
Hunter McGuire Doles, Norfolk	Frank H. Redwood, C. Lydon Harrell, J. Edwin Wood, Jr.
Robert Case Manchester, Norfolk (M.C., U.S.N.R.)	C. Lydon Harrell, Alfred B. Hodges, Walter B. Martin
John Phillip Lynch, Richmond	Wyndham B. Blanton, Douglas G. Chapman, Walter B. Martin
Gilman Rackley Tyler, Richmond (M.R.C., U.S.A.)	William B. Porter, Harry Walker, Walter B. Martin
WASHINGTON	
Alice Grace Hildebrand, Seattle	Russell M. Wilder, Arlie R. Barnes, Edgar V. Allen, Edwin G. Bannick
Ernest Marvin Tapp, Walla Walla	Franklin C. Cassidy, Edward L. Whitney, Edwin G. Bannick
Joseph Hawkins Low, Yakima (M.R.C., U.S.A.)	Paul J. Lewis, Howard L. Hull, Charles E. Watts
WEST VIRGINIA	
George Paul Heffner, Charleston	Martin L. Bonar, Henry L. Robertson, Albert H. Hoge
Walter Louis Schafer, Wheeling (M.C., U.S.N.R.)	William M. Sheppe, Delivan A. MacGregor, Albert H. Hoge

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Michael W. Shutkin, Milwaukee	Elston L. Belknap, Norbert Enzer, Elmer L. Sevringhaus
Roger Clifton Cantwell, Shawano	Guy W. Carlson, Grant H. Laing, Elmer L. Sevringhaus
Canal Zone	
Elmer Roger Smith, Ancon (M.R.C., U.S.A.)	Samuel M. Browne, Maurice Hardgrove, Gilbert M. Stevenson
Territory of Hawaii	
Harry Loren Arnold, Jr., Honolulu	Stewart E. Doolittle, Hastings H. Walker, Harry L. Arnold
Dominion of Canada	
Ontario	
William Addison Guest, Ottawa	John E. Plunkett, Trenholm L. Fisher, Warren S. Lyman

OBITUARY

ALGERNON BRASHEAR JACKSON

On October 22, 1942, death came suddenly but quietly to Dr. Algernon Brashear Jackson, Washington, D. C., a former Professor of Bacteriology, Preventive Medicine and Public Health at Howard University. The cause of his death was myocarditis due to hypertension.

During Dr. Jackson's forty-one years of service in the medical profession he found time as a hobby to compose music and write short plays and stories. He played well the piano for the enjoyment of his family and friends; his preference was classical music. Dr. Jackson was primarily a physician with the soul of a poet, with many talents of an accomplished musician and popular author. Even though he was the author of more than a score of publications in medical journals, the three books published by him dealt with the less scientific aspects of human life.

Algernon Brashear Jackson, the son of Charles A. and Sarah L. Brashear Jackson, was born May 21, 1878, in Princeton, Indiana. His primary, secondary and collegiate education was received in the schools of Indiana; his medical education was obtained at the Jefferson Medical College of Philadelphia, from which he was graduated in 1901. His medical career had several sides, with organization, administration and health education playing major rôles. He began the practice of medicine at Philadelphia in 1901 and continued until 1921. During these twenty years he spent thirteen of them as assistant surgeon at the Philadelphia Polyclinic Hospital and the Graduate School of Medicine of the University of Pennsylvania. He was one of the founders of the Mercy Hospital of Philadelphia, serving as its Surgeon-in-Chief for fifteen years, and as its Superintendent for nine years. During the first world war he was assigned by the Surgeon General's Office to the activities of training camps with responsibilities directed toward the prevention of venereal diseases.

In 1920, Dr. Jackson married Miss Elizabeth A. Newman, R. N., the daughter of Mr. and Mrs. Harden Newman, of Media, Pennsylvania. The rest of his life was one of marital happiness and mutual appreciation. In 1921, he resigned as Superintendent of the Mercy Hospital of Philadelphia, which had then moved to its present site, to accept an appointment on the faculty of medicine of Howard University. He was a member of the staff of Howard University from 1921 to 1934, when he resigned his position as Professor and Administrative Head of the Department of Bacteriology, Preventive Medicine and Public Health, in order to give full-time service to private practice, confining most of this work to the field of his special interest, gastro-enterology. He was actively engaged in this type of practice when death came, and was improving his basic technic in this field by returning for refresher courses during summer months to the postgraduate schools of the University of Pennsylvania and Columbia University.

Dr. Jackson was one of the founders of the Greek letter fraternity, Sigma Pi Phi, known as the "Boule," whose membership was composed of college graduates only. He traveled widely in the United States and was well known for his public health and health education lectures and writings, especially for those phases where the Negro seemed to be involved. At the request of the National Medical Association and the National Hospital Association, he made a 14,000 mile tour of the Negro hospitals in thirteen southern states in 1929; the report of the findings together with his recommendations for corrections of certain defects did much to improve their standards and recognitions.

In his early medical career he did considerable surgery, operating in the hospitals of Philadelphia and for groups at clinics in other parts of the country. In recognition of his work as a physician and surgeon, administrator, original investigator and contributor to medical literature, he was made a Fellow of the American College of Physicians in 1917. This was one of his most cherished recognitions.

His contributions to medical literature were many; special mention may be given to his widely quoted publications on the results of magnesium sulfate injection in the treatment of rheumatism as early as 1911. The lay public read and benefited greatly by his many press releases on health, written in simple terms for their benefit.

Among his memberships in medical organizations we list the following: Fellow of the American College of Physicians; Member, National Medical Association, National Hospital Association, National Tuberculosis Association, American Public Health Association, John A. Andrew Clinical Society and Medico-Chirurgical Society of the District of Columbia.

Dr. Jackson was an Episcopalian by faith.

HILDRUS A. POINDEXTER, M.D.,
Dean, Howard University.